CONTENTS

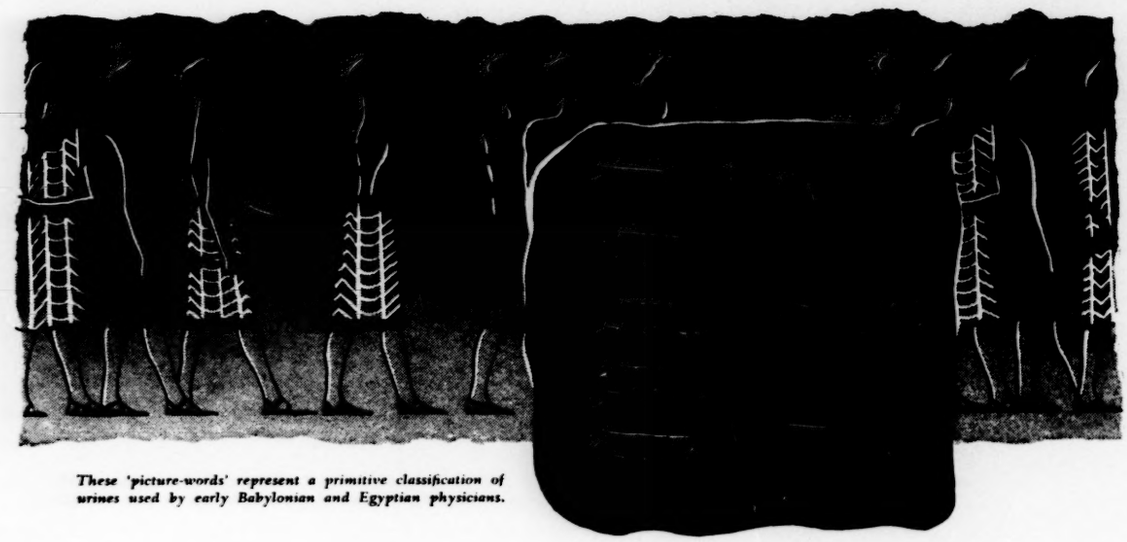
The American Journal of Medicine

VOL. VI JANUARY, 1949 No. 1

Editorial

Clinical Studies

Contents continued on page 5



These 'picture-words' represent a primitive classification of urines used by early Babylonian and Egyptian physicians.

centuries to perfect seconds to perform

When Sumerian and Babylonian physicians, *circa* 4000 B.C., noted the varying colors and constitutions of the "water of the phallus," they were probably not the first uroscopists in history. They were assuredly not the last, for fifty-odd centuries were to elapse before Fehling's first paper on the copper reduction test for urine-sugar appeared in 1848.

But centuries to perfect diagnostic procedures are condensed into seconds to perform the reliable *Clinitest*® method for urine-sugar levels. From start to finish, the test takes less than a minute. This tablet method is simplicity itself . . . readily learned by every diabetic patient. External heating is uniquely eliminated by the *Clinitest* procedure. Routine test interpretation is made easy.

AMES

Clinitest

for urine-sugar analysis

AMES COMPANY

CONTENTS

The American Journal of Medicine

VOL. VI JANUARY, 1949 No. 1

Contents continued from page 3

Review

Seminars on Congestive Failure

Combined Staff Clinics

Clinico-pathologic Conference

Case Report

General Information

THE AMERICAN JOURNAL OF MEDICINE extends an invitation to the profession for original releases on clinical investigations, clinical reviews, case reports and articles designed for postgraduate teaching.

Articles are accepted for publication with the understanding that they are original contributions never previously published. All manuscripts are subject to editorial modification, and upon acceptance become the property of THE AMERICAN JOURNAL OF MEDICINE.

THE AMERICAN JOURNAL OF MEDICINE does not hold itself responsible for any statement made or opinions expressed by any contributor in any article published in its columns.

A reasonable number of illustrations are supplied free of cost; special arrangements must be made with the editor and publishers for excess illustrations and elaborate tables.

Reprints are furnished on order. Prices are quoted on the first day of the month during which article appears. Individual reprints of an article must be obtained from the author.

Change of address must reach us by the 15th of the month preceding month of issue.

PREPARATION OF MANUSCRIPTS

Text. Manuscripts are to be typewritten on one side of the paper, with double spacing and good margins. The original should be sent to the editor and a carbon copy retained by the author.

Illustrations. Illustrations must be in the form of glossy prints or drawings in black ink (*never* in blue). On the back of each illustration the figure number, author's name and an indication of the top of the picture should be given. Legends for illustrations are to be typewritten in a single list, with numbers corresponding to those on the photographs and drawings. Please do not attach legends to the pictures themselves.

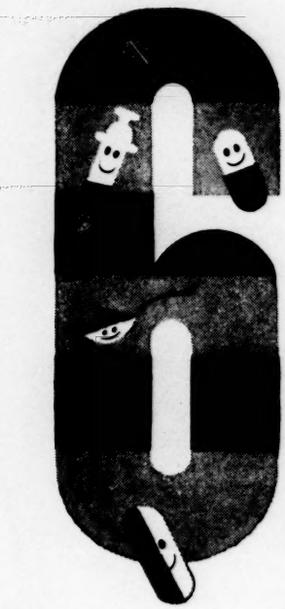
Bibliographies. Bibliographic references should be at the end of the manuscript and not in footnotes. Each reference should include the following information in the order indicated: Name of author with initials; title of article; name of periodical; volume, page and year. The following may be used as a model:

BANCROFT, F. W., STANLEY-BROWN, M. and QUICK, A. J. Postoperative thrombosis and embolism. *Am J. Surg.*, 26: 648, 1945.

The subscription price of THE AMERICAN JOURNAL OF MEDICINE, is $10.00 per year in advance in the United States; $12.00 in Canada and Pan-American countries and $15.00 in foreign countries. Current single numbers $2.00. All Special Numbers $4.00. Prices for such back numbers as are available will be quoted on request.

Address all correspondence to

The American Journal of Medicine · 49 West 45th Street · New York 19



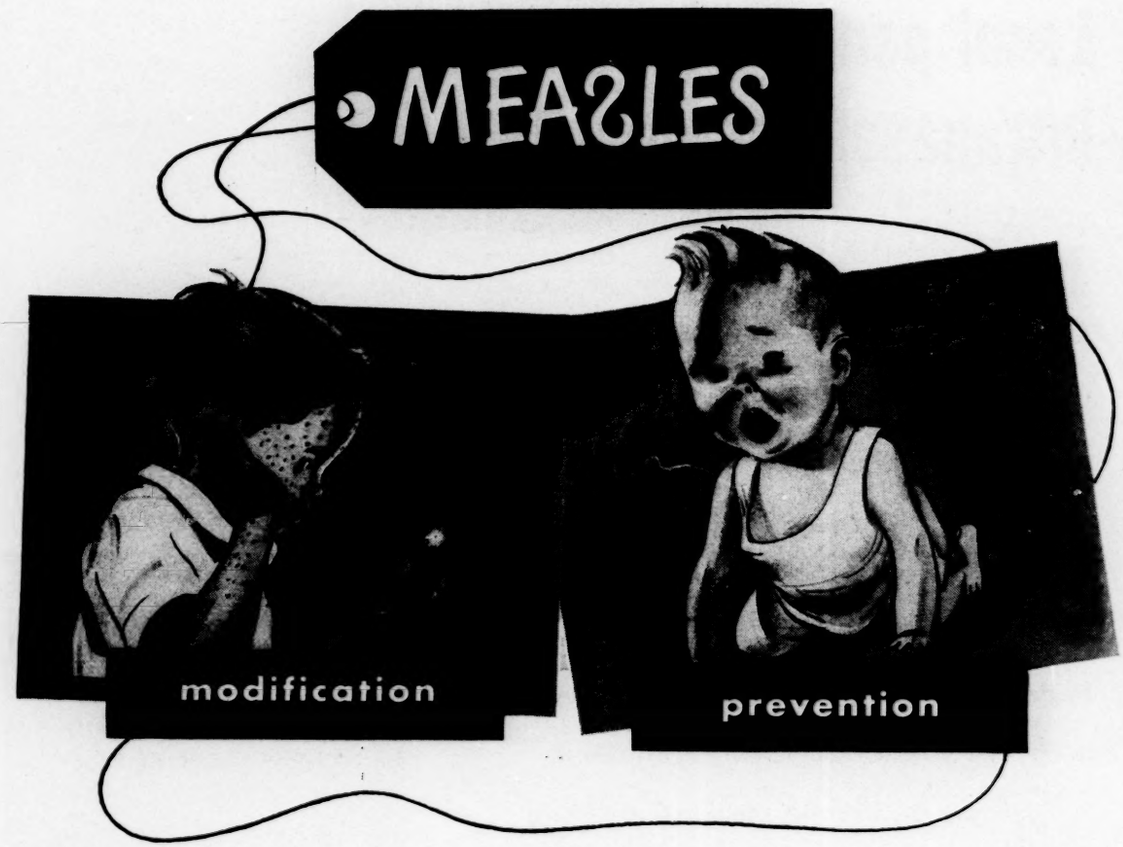
Six of a kind ... *for* 'B' *therapy*

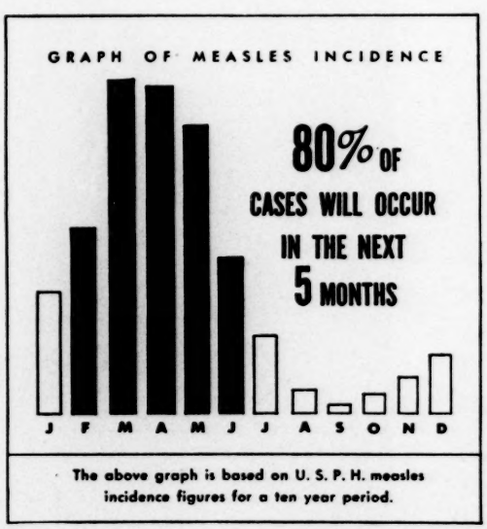
Now ... with the addition of **'Beminal'** fortified with *Iron, Liver and Folic Acid* ... the **'Beminal'** family offers six distinctive forms and potencies. **'Beminal'** fortified with Iron, Liver and Folic Acid will prove especially suitable in the prevention and treatment of iron-deficiency anemias, certain macrocytic anemias, and as adjunctive therapy in pernicious anemia. Beginning with the newest member, the following are the six dosage forms and potencies now available:

1. **'Beminal'** *fortified with Iron, Liver and Folic Acid (Capsules)* no. 821
2. **'Beminal'** *Forte with Vitamin C (Capsules)* no. 817
3. **'Beminal'** *Forte Injectable Dried* no. 495
4. **'Beminal'** *Granules* no. 925
5. **'Beminal'** *fortified with Iron & Liver (Capsules)* no. 816
6. **'Beminal'** *Tablets* no. 815

Ayerst, McKenna & Harrison *Limited* 22 E. 40th St., New York 16

Beminal® *for* 'B' *therapy*





—without fear of side reactions

There's one sure way of silencing crying youngsters and nervous mamas who complain about reactions – specify Cutter Immune Serum Globulin–Human. Successful results with this product are not happenstance. They come from:

1. The right raw material – fresh venous blood from normal donors.
2. The water-clarity of a hemolysis-free and non-pyrogenic product.
3. The concentration of 160 mgm. per cc. of gamma globulin – maintains consistent globulin potency yet permits low volume adjustable dosage:

For prevention–
0.1 cc. Immune Serum Globulin
For modification–
0.02 cc. Immune Serum Globulin
} ***intramuscularly, per pound body weight***

Prepare now for measles' peak season just ahead. Notify your pharmacist the amount of gamma globulin you expect to use—and specify Cutter.

CUTTER LABORATORIES • BERKELEY 10, CALIFORNIA

Prevent or modify measles with–

IMMUNE SERUM GLOBULIN

CUTTER

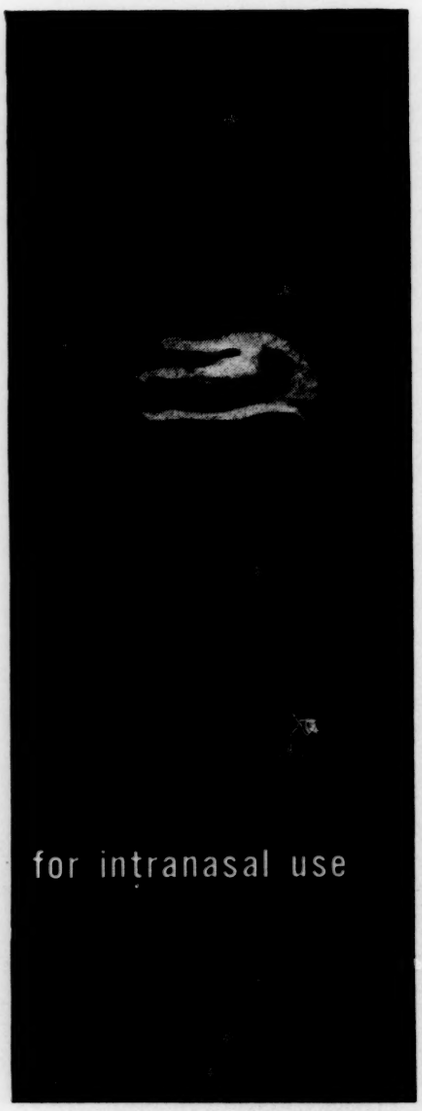
Local penicillin reduced intranasal bacteria 99%

Proceedings of the Society of American Bacteriologists, 47th general meeting, May 13-17, 1947

A series of patients was treated intranasally with local penicillin, *500 units per cc.*, for 5 consecutive days. At the end of this time, the bacteria count was reduced from an average of 7,363 per cc. of nasal washings to the amazingly low average of 42.

In Par-Pen you have a preparation that combines the potent antibacterial action of penicillin, *500 units per cc.*, with the rapid and prolonged vasoconstriction of 'Paredrine Aqueous'.

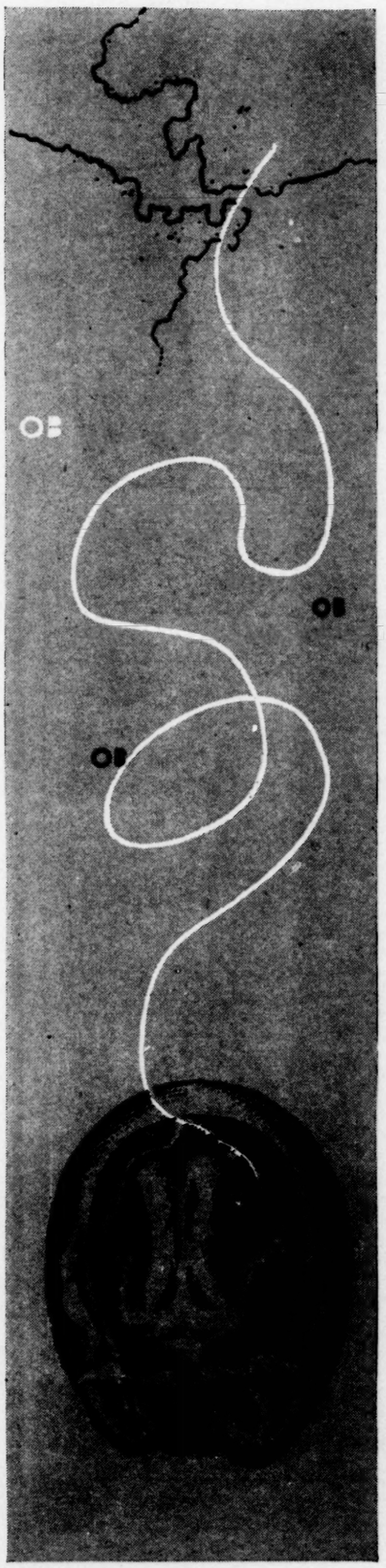
For sample and full information, write Par-Pen on your prescription blank and mail it to us at 429 Arch St., Philadelphia 5, Penna.



Par-Pen

the penicillin-vasoconstrictor combination for intranasal use

Smith, Kline & French Laboratories, Philadelphia



BOTH NATIONS AND UNBORN GENERATIONS ARE DEPENDENT ON LIFE-LINES

WHERE WOULD THE UNITED STATES BE TODAY
WITHOUT THE PANAMA CANAL?
OR THE FETUS
WITHOUT THE UMBILICAL CORD?
THESE CANALS—THESE CHANNELS
TO PROVIDE BOTH NUTRITION AND DEFENSE
HELP ASSURE THE CONTINUANCE OF THAT PRICELESS HERITAGE
OF A HEALTHY SECOND GENERATION.

OBRON is the ℞ of choice to meet the increased needs of both mother and child during gestation and lactation. Study its formula—consider its carefully tested balance. Note the 15 grains of calcium per capsule. Try OBron on your next OB case.

ALL IN ONE CAPSULE

*Dicalcium Phosphate, Anhydrous	768 mg.
Ferrous Sulphate U.S.P.	64.8 mg.
Vitamin A (Fish-Liver Oil)	5,000 U.S.P. Units
Vitamin D (Irradiated Ergosterol)	400 U.S.P. Units
Vitamin B_1 (Thiamine Hydrochloride)	2 mg.
Vitamin B_2 (Riboflavin)	2 mg.
Vitamin B_6 (Pyridoxine Hydrochloride)	0.5 mg.
Vitamin C	37.5 mg.
Niacinamide	20.0 mg.
Calcium Pantothenate	3.0 mg.

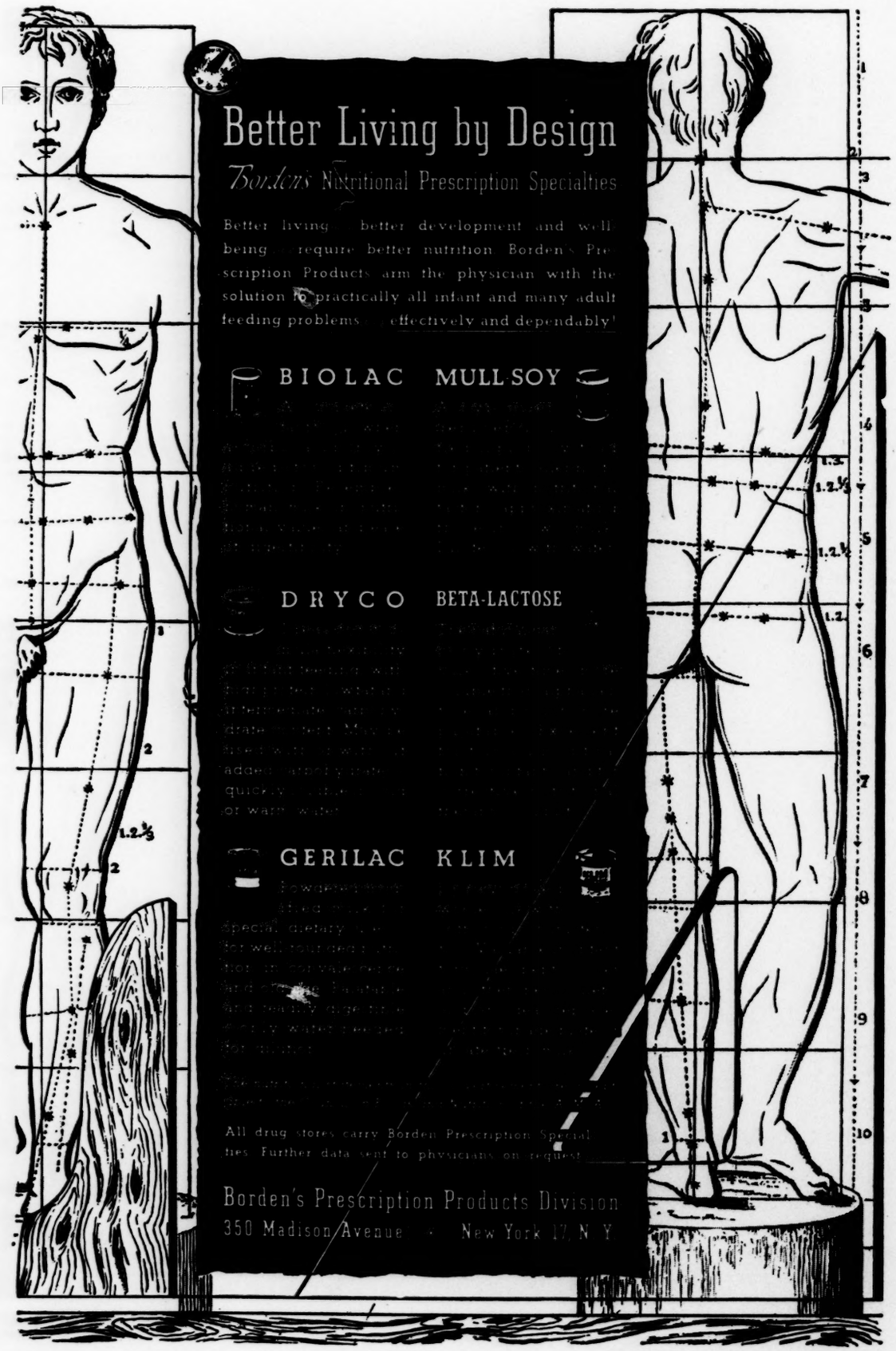
Equivalent to 15 grains Dicalcium Phosphate Dihydrate

ONE OF THE ROERIG BALANCED FORMULAE

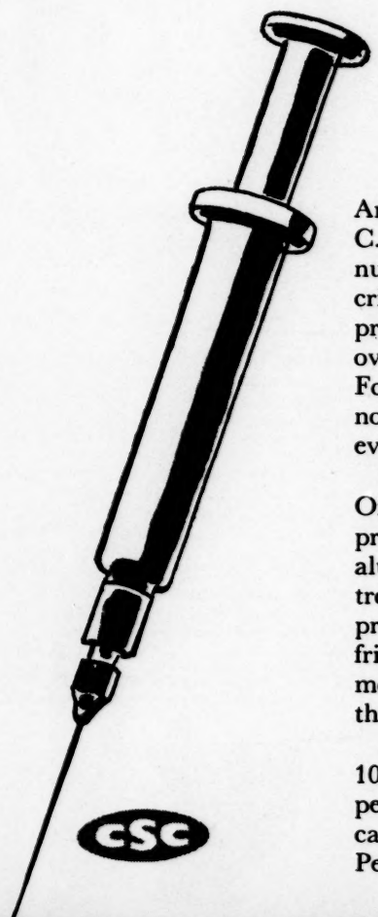
PHARMACEUTICALS ROERIG

Originators of
HEPTUNA • HEPTUNA WITH FOLIC ACID • DARTHRONOL

J. B. ROERIG AND COMPANY
536 LAKE SHORE DRIVE • CHICAGO 11, ILLINOIS


Better Living by Design
Borden's Nutritional Prescription Specialties
Better living — better development and well being — require better nutrition. Borden's Prescription Products arm the physician with the solution to practically all infant and many adult feeding problems — effectively and dependably!
BIOLAC
MULL-SOY
DRYCO
BETA-LACTOSE
GERILAC
KLIM
All drug stores carry Borden Prescription Specialties. Further data sent to physicians on request.
Borden's Prescription Products Division
350 Madison Avenue • New York 17, N. Y.

A Single Injection Every Other Day



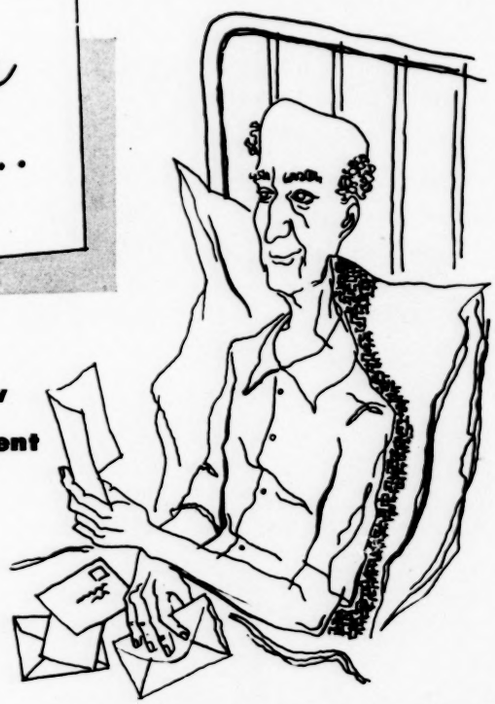
Antibiotic therapy is greatly simplified when C.S.C. Crystalline Procaine Penicillin G in Peanut Oil with aluminum monostearate is precribed. A single 1 cc. injection (300,000 units) produces therapeutic blood levels for 96 hours in over 90% of patients, *and for 48 hours in all patients.* For certainty of therapy, this preparation need not be given, as a rule, more often than once every other day.

Crystalline Procaine Penicillin G in Peanut Oil-C.S.C. contains 300,000 units of micronized procaine penicillin per cc., together with 2% aluminum monostearate for producing a thixotropic suspension. This outstanding penicillin preparation is free flowing and requires no refrigeration. It is indicated in the treatment of most infectious diseases amenable to penicillin therapy.

Available at all pharmacies in economical 10 cc. size rubber-stoppered vials (300,000 units per cc.), and in 1 cc. size (300,000 units) glass cartridges for use in the C.S.C. Disposable and Permanent Syringes.

C.S.C. Pharmaceuticals

A DIVISION OF COMMERCIAL SOLVENTS CORPORATION, 17 EAST 42ND STREET, NEW YORK 17, NEW YORK



with this new
3-tablet-a-day treatment
for secondary anemias

When a patient needs supplementary vitamins as well as iron, as is frequently the case in anemias complicated by prolonged or severe illness, chronic blood loss and poor nutritional history, IBEROL tablets provide multiple therapy in convenient form. Only one IBEROL tablet t.i.d. with meals is enough for the average patient—as the formula shows.

Moderate size is achieved by using the ferrous sulfate as one of the two subcoats which seal the core of the tablet. Agreeable odor and taste come from the outer sugar coating. Capsule shape makes IBEROL easy to swallow. And smaller daily dosage makes IBEROL comparatively economical for the patient.

Combined iron and nutritional factors suggest the effectiveness of IBEROL in both secondary and nutritional anemias, as well as for prophylaxis in pregnancy, old age, surgical after-care and similar conditions. IBEROL is available through your pharmacy in bottles of 100, 500 and 1000 sugar-coated tablets. ABBOTT LABORATORIES, North Chicago, Illinois.

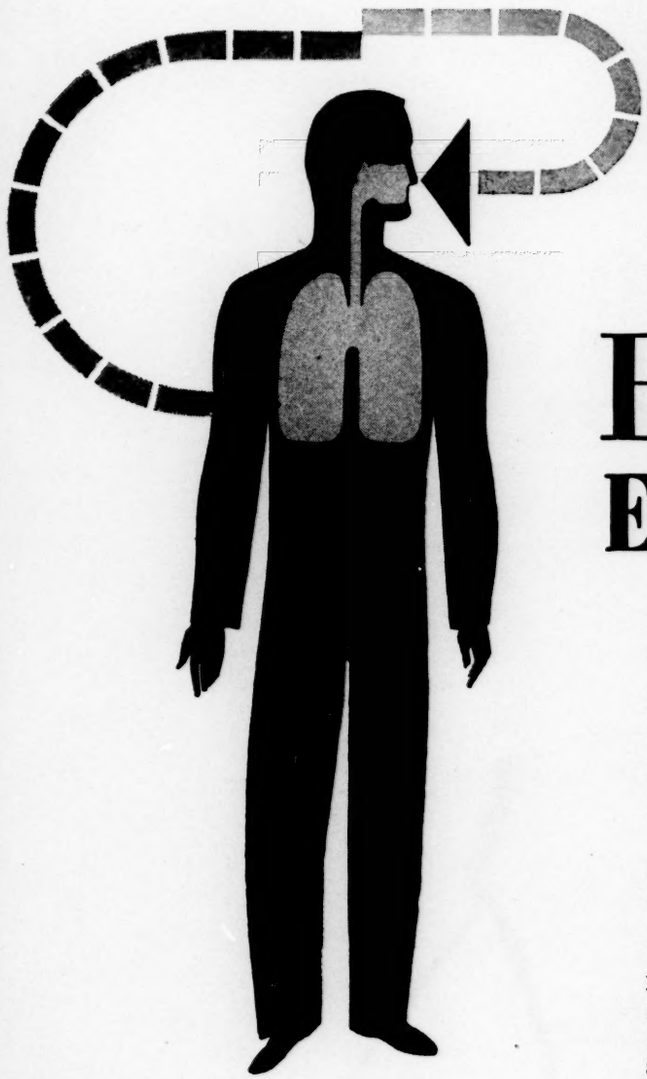
three IBEROL tablets, the daily therapeutic dose for adults, **supply:**

FERROUS SULFATE, U.S.P.	1.05 Gm.
(representing 210 mg. elemental iron, the active ingredient for the increase of hemoglobin in the treatment of iron-deficiency anemia.)	
plus these nutritional constituents:	
Folic Acid	5.1 mg.
Thiamine Hydrochloride	6 mg. (6 x MDR*)
Riboflavin	6 mg. (3 x MDR*)
Nicotinamide	30 mg. (1½ x RDA†)
Ascorbic Acid	150 mg. (5 x MDR*)
Pyridoxine Hydrochloride	3 mg.
Pantothenic Acid (as Calcium Pantothenate)	6 mg.
Liver Fraction (boiling water extract)	1.5 Gm.

*Minimum Daily Requirement.
†Recommended Daily Dietary Allowance.

(Iron—Vitamin B Complex—Folic Acid—Liver Fraction, Abbott)

a completely new approach to cough relief



The antispasmodic and decongestant action of **BENYLIN EXPECTORANT** combats cough, relaxes the bronchial tree, diminishes bronchial congestion and alleviates nasal stuffiness, sneezing and lacrimation. Containing no narcotics, **BENYLIN EXPECTORANT** combines Benadryl® hydrochloride, 10 mg. per teaspoonful, with other remedial agents for safe, effective control of coughs due to colds as well as those of allergic origin.

BENYLIN® EXPECTORANT

promotes liquefaction and removal of mucous secretions from the respiratory tract. The demulcent action of its vehicle soothes irritated mucosa. Acceptable alike to children and adults, its pleasant, mildly tart taste avoids the objections to cloying, overly-sweet preparations.

DOSAGE: One or two teaspoonfuls every two to three hours, as soon as possible following appearance of symptoms. Children, ½ to one teaspoonful every three hours.

BENYLIN EXPECTORANT contains in each fluid ounce:

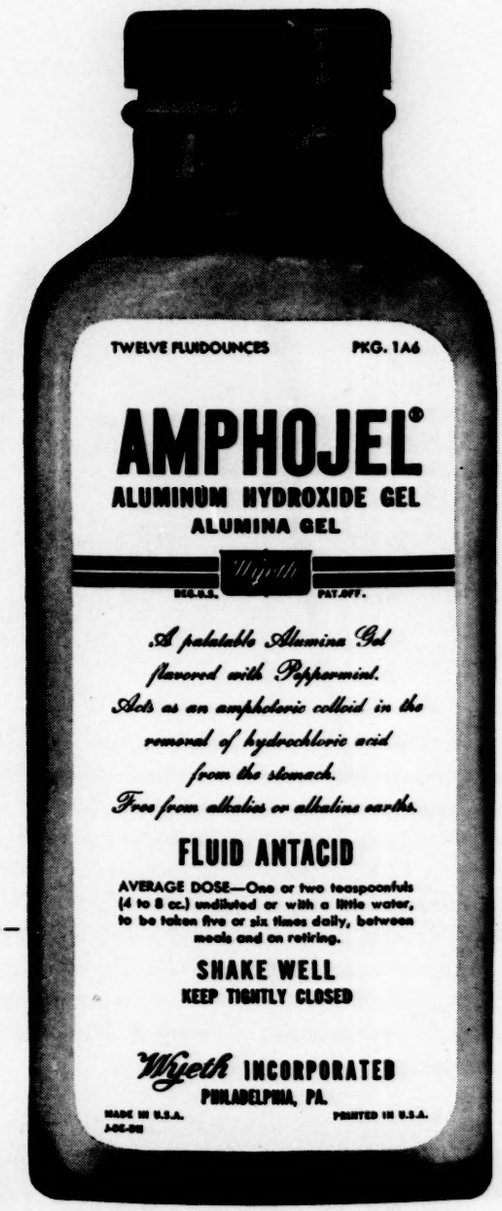
Benadryl Hydrochloride (diphenhydramine hydrochloride, P. D. & Co.)	80 mg.
Ammonium Chloride	12 gr.
Sodium Citrate	5 gr.
Chloroform	2 gr.
Menthol	1/10 gr.

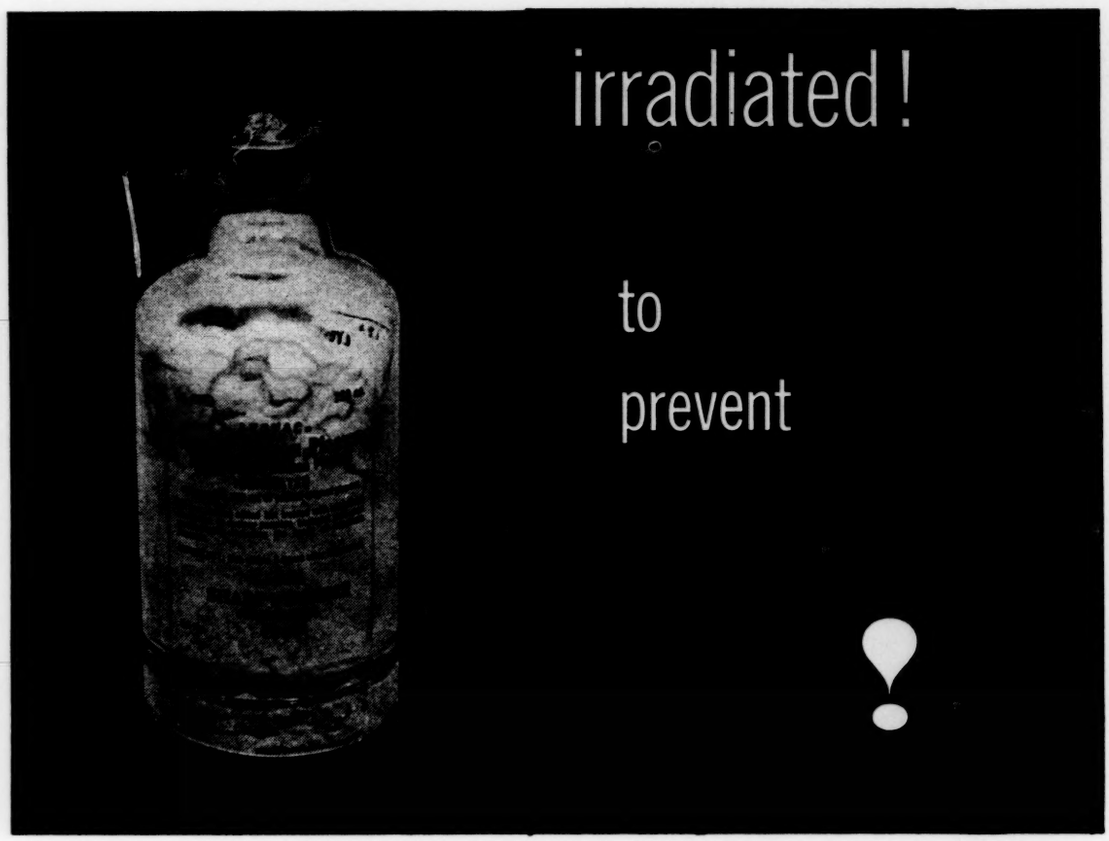
BENYLIN EXPECTORANT is supplied in 16-oz. and gallon bottles.

PARKE, DAVIS & COMPANY • DETROIT 32, MICHIGAN

MEDICAMENTA VERA · PD & CO.

IN THE MEDICAL MANAGEMENT OF PEPTIC ULCER


TWELVE FLUIDOUNCES
PKG. 1A6
AMPHOJEL®
ALUMINUM HYDROXIDE GEL
ALUMINA GEL
Wyeth
REG. U.S.
PAT. OFF.
A palatable Alumina Gel
flavored with Peppermint.
Acts as an amphoteric colloid in the
removal of hydrochloric acid
from the stomach.
Free from alkalies or alkaline earths.
FLUID ANTACID
AVERAGE DOSE—One or two teaspoonfuls
(4 to 8 cc.) undiluted or with a little water,
to be taken five or six times daily, between
meals and on retiring.
SHAKE WELL
KEEP TIGHTLY CLOSED
Wyeth INCORPORATED
PHILADELPHIA, PA.
MADE IN U.S.A.
PRINTED IN U.S.A.



Ultraviolet irradiation of plasma destroys not only all bacteria but also any viral contaminants that might cause homologous serum hepatitis. • You may therefore administer *irradiated* LYOVAC *plasma* without danger of hepatitis. • Stable, portable LYOVAC Normal Human Plasma (*Irradiated*) is prepared from fresh, citrated, human blood of healthy donors, according to regulations of the National Institute of Health. The plasma is pooled, flash frozen, *dehydrated from the frozen state under high vacuum* (lyophile process), and sealed under vacuum. • *Blood substitute of choice for emergencies*, irradiated LYOVAC plasma is quickly restored, needs no typing or crossmatching, and each unit is osmotically equivalent to two units of whole blood. • LYOVAC Normal Human Plasma (*Irradiated*) is supplied in vacuum bottles to yield 50 cc., 250 cc. and 500 cc. of restored, *irradiated* normal plasma, or smaller quantities of *hypertonic* plasma. Sharp & Dohme, Philadelphia 1, Pa.

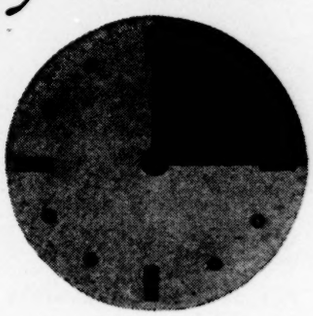
Lyovac®

SHARP & DOHME

Normal Human Plasma IRRADIATED

Penicillin Protection by the Calendar

not by the clock



when you use

Flo-Cillin "96"

Bristol Laboratories Trademark For
CRYSTALLINE PROCAINE PENICILLIN G IN OIL
(300,000 units per cc.)
With Aluminum Monostearate, 2%

This remarkable development in repository penicillin therapy ends the need for *daily* injections. A single injection of 1 cc. produces therapeutic blood levels lasting 96 hours (4 days) in 90% of patients. A single injection *every other day* is considered adequate for most clinical purposes. Exceptionally severe conditions may require more frequent dosage.

Bristol
LABORATORIES INC
SYRACUSE, NEW YORK

Constantly Fluid · Requires No Prolonged Shaking · Will Not Clog the Needle

westsal MARK

the only salt substitute that tastes exactly like salt

westsal is a joy to patients on low-salt (sodium) diets. It's the *only* salt substitute that makes food taste *exactly* as if seasoned with salt. No bitter, no disagreeable taste. Used freely at the table—in cooking and baking. ● Sodium-free, safe, convenient, ***westsal*** assures eating without cheating, a minimum intake of harmful sodium, better nourishment, and grateful, happier, patients in . . .

congestive heart failure • hypertension • toxemias of pregnancy

send for tasting samples →

westsal is a solution of lithium chloride with small amounts of citric acid and potassium iodide (iodizing traces). Bottles of 2¼ oz.

WESTWOOD PHARMACEUTICALS, Dept. AM . 468 Dewitt St., Buffalo 13, N. Y.
division of Foster-Milburn Co.

The dihydro form of streptomycin

Dihydrostreptomycin Squibb
HYDROCHLORIDE

PERMITS HIGHER DOSAGE FOR MORE PROLONGED PERIODS

WHAT IS IT?

A potent antibiotic compound derived from streptomycin by reduction with hydrogen.

WHEN IS IT INDICATED?

Like streptomycin, as an adjunct to other measures in tuberculosis.

HOW DOES IT ACT?

The antibacterial activity of Dihydrostreptomycin usually parallels that of streptomycin in tuberculosis. Resistant strains of organisms appear to develop as rapidly as with streptomycin.

WHAT ARE ITS ADVANTAGES?

Dihydrostreptomycin is significantly less neurotoxic than streptomycin and hence can be given in larger doses and for more prolonged periods. In addition, patients showing allergic reactions to streptomycin have been able to continue with the dihydro form.

HOW IS IT ADMINISTERED?

Only intramuscularly, pending further clinical studies.

WHAT IS THE DOSAGE?

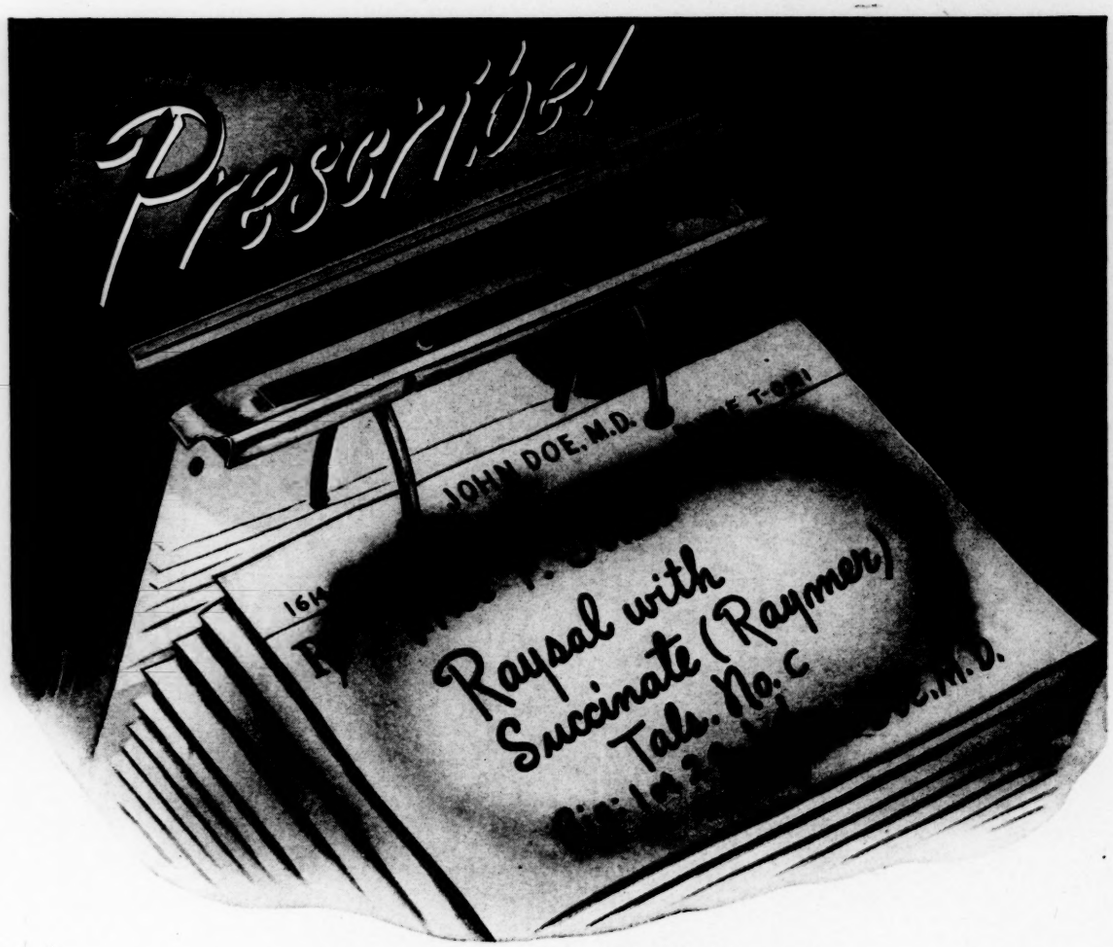
Daily doses of 2 grams of Dihydrostreptomycin Squibb may be given safely for periods equal to those in which streptomycin has been restricted to 1 gram a day, provided there is no renal dysfunction. Average dosage—1 to 2 grams daily in divided doses every 12 hours.

HOW SUPPLIED?

20 cc. vials containing the equivalent of 1 Gm. streptomycin base
50 cc. vials containing the equivalent of 5 Gm. streptomycin base

E. R. Squibb & Sons, New York 22, N. Y.

SQUIBB *a leader in antibiotic research and manufacture*



for the Treatment of

ARTHRITIS and RHEUMATISM

RAYSAL WITH SUCCINATE . . . The *ethical* salicylate-succinate formula . . . Employs three principal ingredients—salicylate, iodine, and succinate . . . designed to combine the almost specific antiarthritic and antirheumatic action of the salicylates, the stimulating and nutritionally corrective effects of iodine and the salicylate detoxifying action of succinic acid.

An ideal companion medication for other therapeutic measures employed in arthritis and rheumatism. RAYSAL WITH SUCCINATE will enhance the efficiency of RAY-FORMOSIL . . . a safe and effective combination for use in your next case. Sample and literature will be sent upon request.

The Detoxified Salicylate Medicament

ENTERIC COATED TABLETS (SALOL)

Raysal.....5 grains
(Representing 43% Salicylic Acid and 3% Iodine in Calcium-Sodium Phosphate Buffer Salt Combination)
Succinic Acid.....2 grains

RAYMER

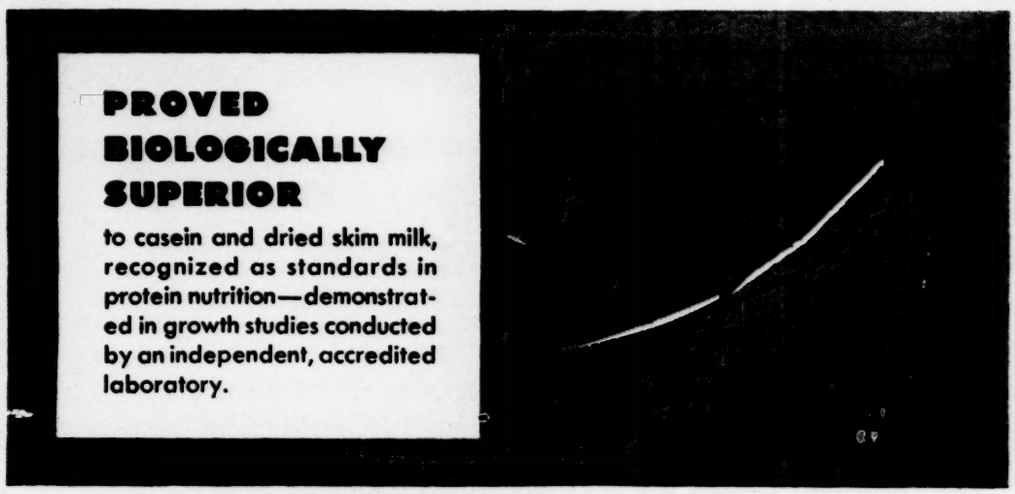
Available for office use and at your pharmacy on prescription

PHARMACAL COMPANY • PHILADELPHIA 34, PA.
PHARMACEUTICAL MANUFACTURERS

Over a Quarter Century Serving Physicians

PROTOPLEX

Whole Mixed Protein plus Whole Liver and Yeast



PROTOPLEX* provides all the essential and nonessential amino acids as present in casein, lactalbumin, primary dried yeast U.S.P., and desiccated whole liver. Relatively salt- and fat-free.

Delicious — **Eaten like cereal...may also be incorporated in cakes, biscuits, and waffle batters.**

Excellent Tolerance — **An extra 50 to 100 grams of protein daily easily administered.**

SUPPLIED: In 1-lb. packages, available through your local pharmacist.

*Exclusive trademark of Walker Vitamin Products, Inc.

Walker **VITAMIN PRODUCTS, INC., MOUNT VERNON, N. Y.**

NEW EFFECTIVE HEMATINIC

Laurium

provides readily available iron for the anemia patient.

Gastrointestinal symptoms are notably absent, since the source of iron in Laurium is ferrous gluconate — readily absorbed, well utilized, better tolerated.

In treatment of iron deficiency and nutritional anemias — despite the qualitative and quantitative adequacy of the iron prescribed — the conversion of iron salts to hemoglobin may be balked by absence of necessary hemopoietic adjuncts. Laurium is fortified with adjunctive hematinic principles that

promote utilization of iron
stimulate erythropoiesis
correct concomitant vitamin deficiencies

Laurium

Administration—As a dietary supplement, one or two capsules daily.

In the treatment of hypochromic or nutritional anemia, one or two capsules three times daily as required by the severity of the anemia and the response to therapy.

Laurium

Each capsule contains:

Ferrous Gluconate	280 mg.
Liver Concentrate (1:20)	200 mg.
(Equivalent — 4 Gm. Fresh Liver)	
Folic Acid	1 mg.
Thiamine Hydrochloride	2 mg.
Riboflavin	1 mg.
Niacinamide	10 mg.
Ascorbic Acid	15 mg.

Each capsule contains approximately 33 mg. of elemental iron—three times the Minimum Daily Adult Requirement—two times the M.D.R. for thiamine, one-half the M.D.R. for riboflavin and ascorbic acid, with 10 mg. of niacinamide. The need for folic acid in human nutrition has not been established.

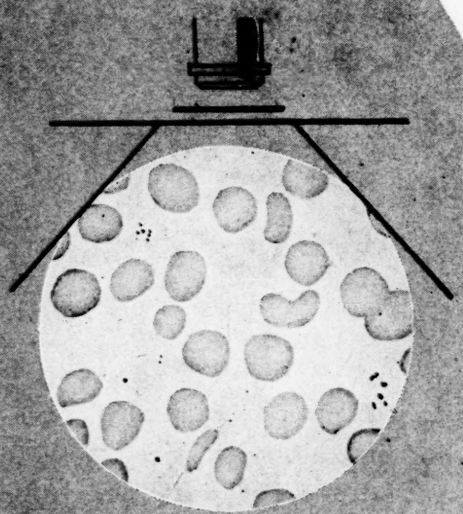
Laurium: supplied in bottles of 100 capsules.

Whittier

LABORATORIES

Division Nutrition Research Laboratories

Chicago 30, Illinois



LIVITAMIN WITH IRON

The Blood Picture Responds More Quickly

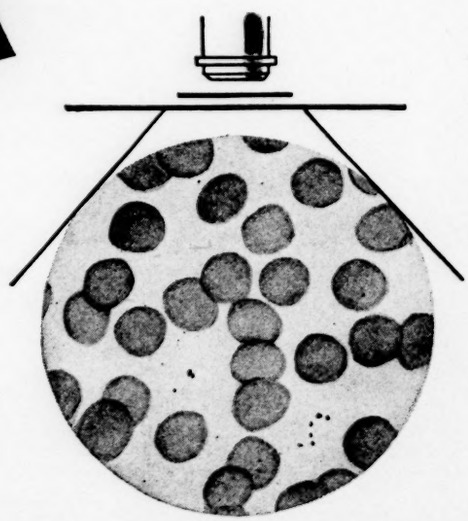
While iron is essential for hemopoiesis, recent findings give evidence of the important role in blood formation played by B-complex vitamins and certain factors occurring in fresh liver concentrate. This approach may be considered as "Supported Therapy," from which rapid correction of both the blood picture and the systemic manifestations of anemia may be expected.

Livitamin with Iron is indicated in hypochromic anemias regardless of origin and routinely during pregnancy and lactation. Its liquid form and palatable taste make it especially valuable for administration to children. Adult dose, 3 to 4 teaspoonfuls 3 times daily.

This is the Formula:

Each fluidounce of Livitamin with Iron, prepared with an attractive, palatable vehicle, presents:

Iron and Manganese Peptonized..30 gr.
(Equiv. to 45 mg. elementary Iron)
Iron Peptonized, N.F.....12½ gr.
(Equiv. to 140 mg. elementary Iron)
Thiamine Hydrochloride (B_1)..10 mg.
Riboflavin (B_2, G).....5 mg.
Nicotinamide (Niacinamide)...25 mg.
Pyridoxine Hydrochloride (B_6)..1 mg.
Pantothenic Acid.....5 mg.
Liver Concentrate 1:20.....45 gr.
(Represents 2 oz. fresh liver)
Rice Bran Extract.....15 gr.



THE S. E. MASSENGILL COMPANY
Bristol, Tenn.-Va.
NEW YORK · SAN FRANCISCO · KANSAS CITY

SEMCO

Gentlemen:

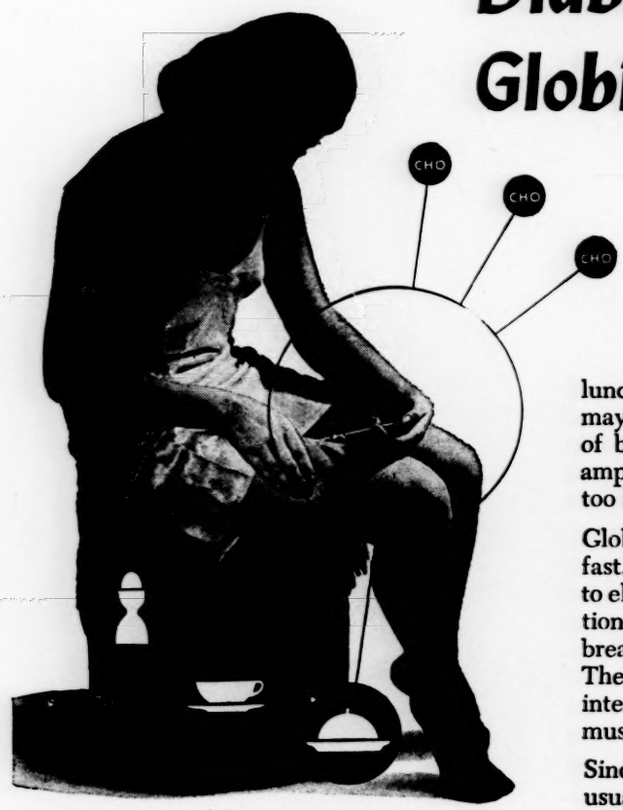
Please send, without charge, the new illustrated brochure on clinical findings of Vertavis in hypertension.

..... M.D.

ADDRESS .....

CITY ..... ZONE ..... STATE .....

Diabetes, diet and Globin Insulin . . .



THE ADVANTAGES of one-injection control of diabetes can, through adjustment of diet and dosage, be made available to the majority of patients requiring insulin. In view of the convenience and freedom afforded by the unique intermediate action of 'Wellcome' Globin Insulin with Zinc, the necessary adjustment is well worth while. Though not a complicated procedure, the regulation of carbohydrate balance warrants reiteration because of its importance:

SOME FACTS ABOUT DIETARY ADJUSTMENT: The distribution of carbohydrate in the meals must be adjusted in accord with the type of action exhibited by Globin Insulin, which is intermediate between regular and protamine zinc insulin. Proper carbohydrate distribution with proper insulin timing is essential; lack of balance may lead to poor control or to an erroneous impression of the characteristics of Globin Insulin.

A good carbohydrate distribution for the patient on Globin Insulin is to divide the total carbohydrate per day into 1/5 at breakfast, 2/5 at lunch and 2/5 at suppertime. This initial diet may be adjusted in accord with the indications of blood sugar levels and urinalyses. (For example, a low blood sugar before supper indicates too little carbohydrate for lunch or vice versa.)

Globin Insulin is ordinarily given before breakfast. Onset of action is usually sufficiently rapid to eliminate the need for a supplementary injection of regular insulin. However, the amount of breakfast carbohydrate should not be too large. The right amount, as well as the optimal time interval between the injection and breakfast, must of course be determined for each patient.

Since the maximum action of Globin Insulin usually occurs in the afternoon or early evening, hypoglycemia is sometimes noted at this time. As a guard against it, the carbohydrate content of the noon meal may be increased, or a midafternoon lunch provided. Thus the original distribution of 1/5, 2/5 and 2/5 might, for example, require adjustment to 2/10, 5/10 and 3/10 or to 2/10, 4/10, 1/10 and 3/10. Once the balance of carbohydrate intake and insulin timing has been established, the patient must be impressed with the importance of adhering to the regimen.

'Wellcome' Globin Insulin with Zinc is a clear solution, comparable to regular insulin in its freedom from allergenic properties. Available in 40 and 80 units per cc., vials of 10 cc. Accepted by the Council on Pharmacy and Chemistry, American Medical Association. Developed in The Wellcome Research Laboratories, Tuckahoe, New York. U.S. Patent No. 2,161,198. LITERATURE ON REQUEST.

'Wellcome' Trademark Registered

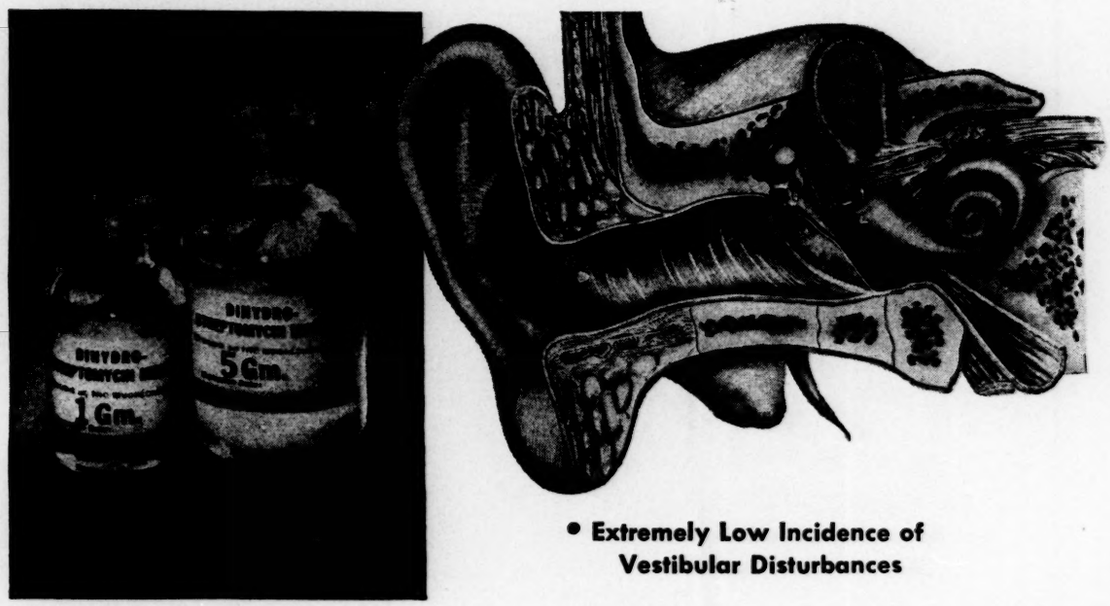
WELLCOME
Globin Insulin
WITH ZINC

BURROUGHS WELLCOME & CO. (U.S.A.) INC., 9 & 11 EAST 41ST STREET, NEW YORK 17, N.Y.

Announcing...

DIHYDROSTREPTOMYCIN

A New, Dramatic Advance In Antibiotic Therapy



- **Extremely Low Incidence of Vestibular Disturbances**
- **Less Frequent Allergic Manifestations**
- **Unsurpassed Purity**
- **Undiminished Antibacterial Activity against *Mycobacterium tuberculosis***

Dihydrostreptomycin Merck is a new, highly purified antibiotic, chemically distinct from streptomycin, and characterized by greatly reduced neurotoxicity.

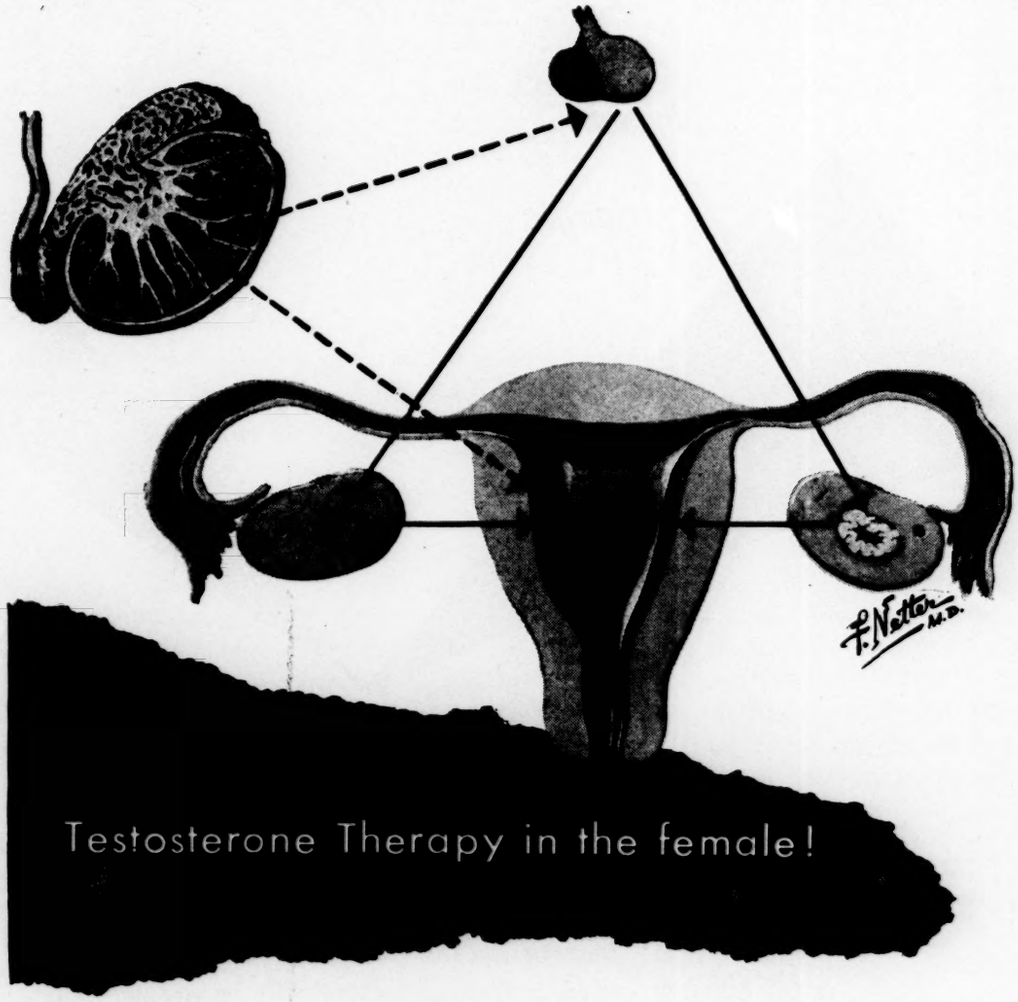
Allergic manifestations due to dihydrostreptomycin therapy are rare, and no local skin irritation or other allergic phenomena have been reported thus far among personnel who frequently handle this drug.

Dihydrostreptomycin Merck and Streptomycin Calcium Chloride Complex Merck may be used interchangeably in the treatment of tuberculosis.

DIHYDROSTREPTOMYCIN
MERCK
(supplied as the sulfate or the hydrochloride)

MERCK

MERCK & CO., Inc. *Manufacturing Chemists* **RAHWAY, N. J.**



Testosterone Therapy in the female!

Paradoxically, Testosterone, the male sex hormone, has clinical application in women. Theoretically, the menopausal syndrome, dysmenorrhea, and functional bleeding should be corrected by proper therapy with follicular hormone, progesterone, or pituitary gonadotropin.

Testosterone Armour

often is effective when, in actual practice, some cases of these syndromes do not respond to the above therapy.

Available in these three forms:

Testosterone Propionate Armour . . . (for injection) 25 milligrams per cc. in packages of 6—1 cc. ampules, 50—1 cc. ampules, 1—10 cc. vial.

Methyl Testosterone Armour . . . (oral) 25 milligrams per tablet—in boxes of 30 and 100 tablets.

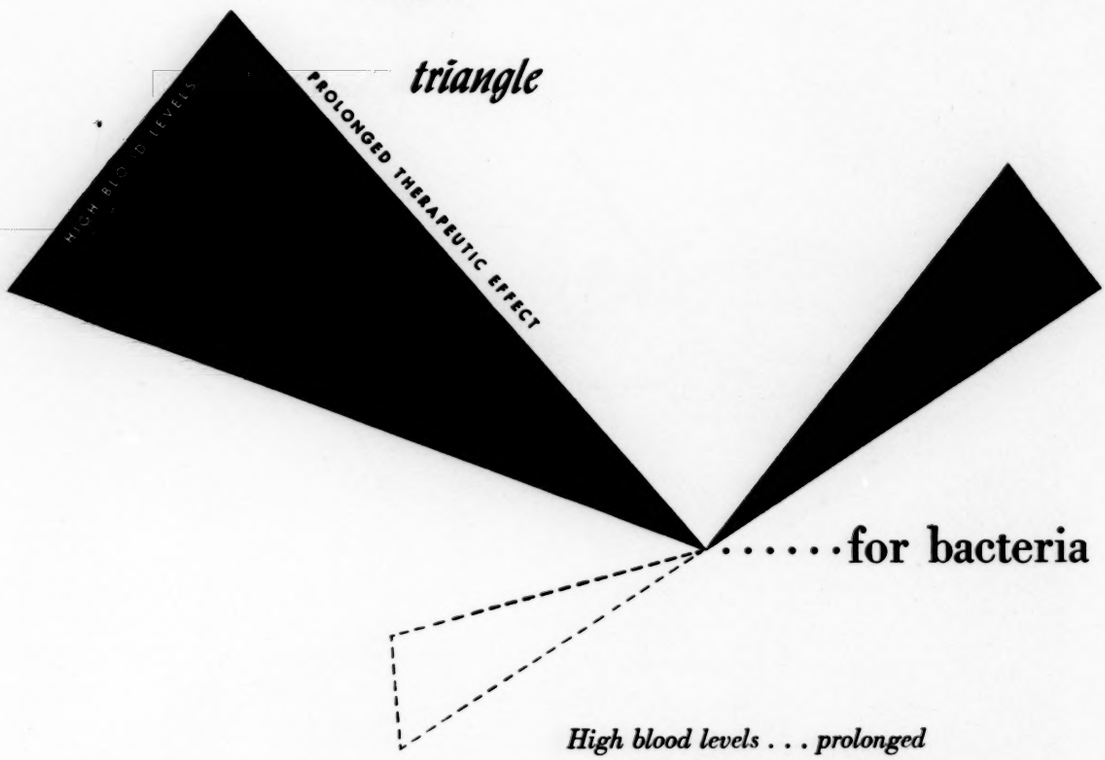
Testosterone Pellets Armour . . . (for subcutaneous implantation) 75 milligrams per pellet—in boxes of 3.

Have confidence in the preparation you prescribe—specify "ARMOUR"

ARMOUR Laboratories

HEADQUARTERS FOR MEDICINALS OF ANIMAL ORIGIN • CHICAGO 9, ILLINOIS

vicious triangle



High blood levels . . . prolonged therapeutic effect . . . characterize 'Duracillin, In Oil' (Crystalline Procaine Penicillin—G in Oil, Lilly). To overwhelm invading bacteria, effective penicillin blood levels must be maintained around the clock. 'Duracillin, In Oil,' is more than adequate to do the job. An injection of 1 cc. (300,000 units) of 'Duracillin, In Oil,' assures, for at least twenty-four hours, blood concentrations of penicillin that are sufficient to subdue most of the virulent penicillin-susceptible organisms. Repeating the 1-cc. dose at twenty-four-hour intervals is all that is required to keep most invading pathogens "on the run." Specify 'Duracillin, In Oil,' in 1-cc. or 10-cc. rubber-stoppered ampoules. No refrigeration is necessary.*

*See "Clinical Evaluation of 'Duracillin, In Oil,'" *Physician's Bulletin*, September-October, 1948.

The American Journal of Medicine

VOL. VI JANUARY, 1949 NO. 1

Editorial

The Manner of Expressing Serum Protein Values

NOT infrequently in medicine the early manner of expressing the value or result of a test becomes established by custom and persists long after it has outlived its usefulness, no longer reflects the true meaning of the determination or is actually misleading. A classic example is the content or concentration of hemoglobin in the blood which still continues in many instances to be expressed in percentages of a theoretic and misleading normal rather than in terms of the actual amount per unit of blood even though often determined on that basis.

Another and more recent example is that of serum or plasma proteins. Analysis of serum or plasma for protein usually includes a determination of the total protein and the albumin fraction, the globulin fraction being determined by difference between total protein and albumin. Occasionally, the fibrinogen is determined also. Values are expressed as Gm. of total protein per 100 cc. of serum or plasma, Gm. of albumin and Gm. of globulin. Commonly, another value is expressed, namely, the ratio of albumin to globulin or the A/G ratio. Unfortunately, too often the total protein value and the A/G ratio alone are given, with the expression A/G ratio "normal" or A/G ratio "reversed," without the actual value for the albumin and globulin. This is particularly apt to occur in the publication of the results of clinical research, in case reports and in the presentation of patients and case records at ward rounds, clinical pathologic conferences and other teaching exercises. In addition to the simple error of omission committed by this procedure, it indicates on the part of the user a lack of proper appreciation of the true value and meaning of this determination or test.

As is well known, the albumin portion of the serum or plasma protein normally constitutes about three-quarters of the total, so that the ratio of albumin to globulin is in the neighborhood of 2:1 or 3:1. In the earlier days of determination of the plasma or serum proteins the increase in globulin to amounts equal to that of the albumin or even greater was observed and constituted an obvious abnormality which attracted considerable attention. From this, then, arose the interest in the ratio between the two fractions, and the custom of expressing the results of the determination in terms of the "ratio" rather than the actual amounts of albumin and globulin.

Such emphasis on the ratio of albumin to globulin is incorrect and improper because it leads to neglect of the actual values for albumin and globulin, both in thought and expression. While alterations in the ratio are significant, the actual concentrations of albumin and globulin are much more important. They have not only more meaning but a different meaning. The reason for this is clear. The amount of

albumin can vary up or down independently of the globulin as the result of any one of a number of abnormal conditions. The same is true of globulin in relation to albumin. The total protein is a resultant of the sum of the albumin and globulin. It, therefore, varies up or down or may even fail to change, despite the presence of abnormalities affecting the amounts of albumin, globulin or both, depending on the magnitude and direction of such change. A reversal of the albumin/globulin ratio with an albumin of 4.5 Gm. and a globulin of 6.0 Gm., as may occur in lymphopathia venereum, has a meaning much different from a reversal of the ratio with an albumin of 1.5 Gm. and globulin of 3.0 Gm. such as may be found in nephrosis. In the former instance the albumin is normal but the globulin considerably increased. In the second instance the albumin is greatly reduced but the globulin is normal. In both instances the albumin/globulin ratio is reversed, but the significance and meaning of the reversal are entirely different.

The examples cited are rather gross. There are other situations in which the variations and their meanings are much more subtle. There is, for instance, the slightly elevated globulin in some cases of nutritional hypoproteinemia which may mask a slight but significant hypo-albuminemia if attention is paid only to totals and ratios. There is the effect of infection on the globulin which causes the same error. The hypo-albuminemia of mild liver disease may be missed unless the amounts of the two fractions are known, and decreases in albumin may in turn hide from view a significant increase in the globulin.

It can be seen clearly, then, that from this point of view the most important clinical aspect of the serum proteins is the amount or concentration of the two fractions, and that the ratio of albumin to globulin, while interesting, is of much less importance and may be actually misleading unless one knows or is told the amounts of the two protein fractions. In particular, this is true of the globulin. It, more than albumin, is subject to deviations in both directions from the normal. Changes in it, especially excesses, may provide an important clue to some of the more unusual and uncommon diseases, otherwise less likely to be suspected. Increases in the globulin fraction occurring with decreases in the albumin not infrequently mask the latter, without affecting the total protein.

In conclusion, it should be emphasized that while the improper recording or presentation of the results of serum protein determinations, with emphasis on the albumin/globulin ratio, has immediate, practical disadvantages, its most serious effect is on the habit of mind in relation to the diagnostic use of this test. The writer has repeatedly observed failure to recognize or consider diagnostic possibilities based on serum protein determinations because attention was paid to the albumin/globulin ratio only and not to the amounts of individual fractions.

JOHN B. YOUMANS, M.D.

Clinical Studies

The Syndrome of Pulmonary Stenosis with Patent Foramen Ovale*

ARTHUR SELZER, M.D., WILLIAM H. CARNES, M.D., CHARLES A. NOBLE, JR., M.D., WILLIAM H. HIGGINS, JR., M.D. *and* ROBERT O. HOLMES, M.D.

San Francisco, California

THE demonstration by Blalock and Taussig[1] that persistent cyanosis in certain types of congenital cardiac disease can be reduced dramatically by a surgical operation has brought into focus the great practical importance of correct clinical diagnosis of congenital cardiovascular malformations. The great interest in congenital heart disease which has developed in the last decade has therefore shifted recently from the non-cyanotic to the cyanotic group.

A considerable number of malformations of the cardiovascular system are associated with cyanosis. Many of these are not compatible with life for more than a few days or months. A small number of the patients survive until childhood and only very few reach adult life. Maude Abbott[2] stated that nine-tenths of the cases of morbus ceruleus in adults were cases of the tetralogy of Fallot. In the last few years the variation of the tetralogy of Fallot described by Eisenmenger[3] has aroused interest and has been accepted as a clinically recognizable entity. In 1945 Currens, Kinney and White[4] reported eleven cases of still another cyanotic congenital cardiac lesion, namely, pulmonary stenosis with intact interventricular septum and summarized the clinical findings but no consistent diagnostic criteria were established.

Recently we have had the opportunity to observe two cases of pulmonary stenosis with intact interventricular septum and patency of the foramen ovale in adults. The striking similarity of these cases and the fact that neither of them was diagnosed correctly during life prompted us to review similar cases reported in the literature. The findings in all the available autopsied cases have been summarized and contrasted with the clinical and pathologic features of similar congenital cardiac lesions.

CASE REPORTS

CASE 1. W. H. J., a thirty-nine year old white male, entered Stanford University Hospitals on April 24, 1946, because of increasing dyspnea. His past history revealed that there was some question as to whether or not he was a "blue baby" but his early development was normal. At the age of seven he became somewhat dyspneic upon exertion but played normally. At the age of twelve he was forced to drop out of games. In high school he attempted to play football but was unable to do so because of dyspnea.

He never noticed cyanosis until the age of eighteen when he developed slight cyanosis while swimming. During the third decade of life cyanosis was very mild, mostly noticeable upon exertion and he led a relatively normal life working as a tool grinder. At thirty-one there was slight intensification of cyanosis; at thirty-four cyanosis became moderately severe and his activities were markedly curtailed because of dyspnea. This state of affairs was gradually intensified in severity until he was

* From the Departments of Medicine and Pathology, Stanford University School of Medicine, the Divisions of Medicine and Pathology, University of California Medical School and the San Francisco Hospital (Department of Public Health, City and County of San Francisco).

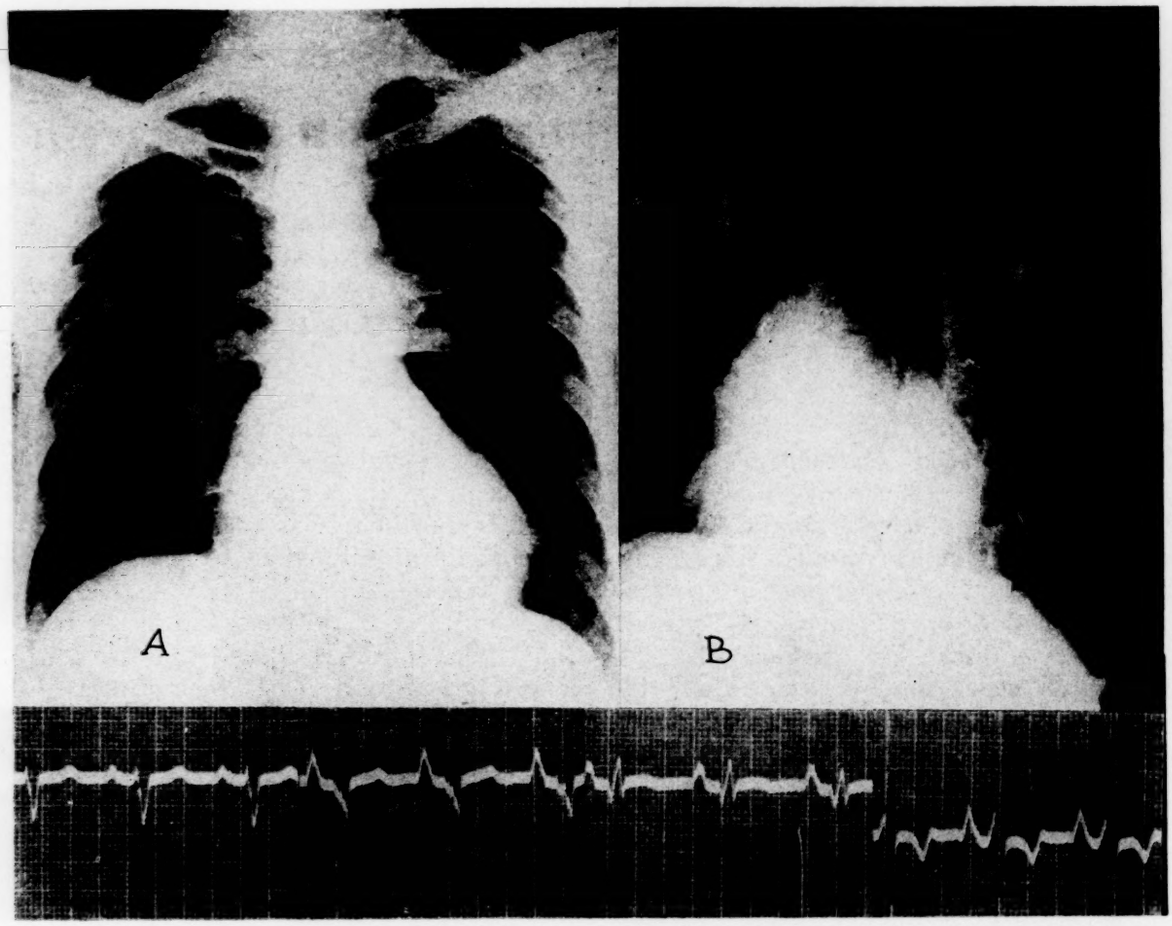


FIG. 1. Roentgenograms and electrocardiogram in Case I. A, postero-anterior view showing slight cardiac enlargement, dilatation of the pulmonary artery and marked dilatation of the left branch. B, left anterior oblique view showing elevation of the apex and a notch indicating the interventricular groove (arrow). C, four-lead electrocardiogram showing prominent P-waves and a pattern of right bundle-branch block.

completely incapacitated and cyanosis became extreme.

Two years before death he developed attacks of vertigo, with nausea, vomiting and occasional hematemesis. He had few questionable convulsions during the last year. About six weeks before death he was bronchoscoped because of marked enlargement of the left hilar shadow in the chest roentgenogram, suspected as representing a possible tumor, and was found to have partial constriction of the left main bronchus from outside pressure.

Examination upon entry to the hospital revealed an extremely cyanotic man with marked clubbing of the fingers and toes. Other pertinent findings included slight cardiac enlargement with a moderately loud systolic murmur at the apical region, somewhat softer at the left sternal border, and faint at the base of the heart. The heart sounds were not remarkable, but both were rather loud and snapping at the base of the heart in a sitting position.

Laboratory findings were as follows: vital capacity, varied between 3.5 and 4 L.; venous pressure, 9 cm. of water, circulation time (arm to tongue) 12 seconds. Blood count: hemoglobin, 189 per cent, red blood cells, 9.4 million, leukocytes, 9,500 with a normal distribution. Urinalysis revealed slight albuminuria, pH 5.5, specific gravity 1.007 and occasional leukocytes and rare erythrocytes in the sediment.

Electrocardiogram showed right axis deviation with QRS complexes widened to 0.11 seconds and notched in all leads. T waves were inverted in leads III and IV_F. There was a tall and prominent P_2. (Fig. 1C.) Chest roentgenogram revealed a normal-sized heart with a somewhat elevated apex of the heart and a

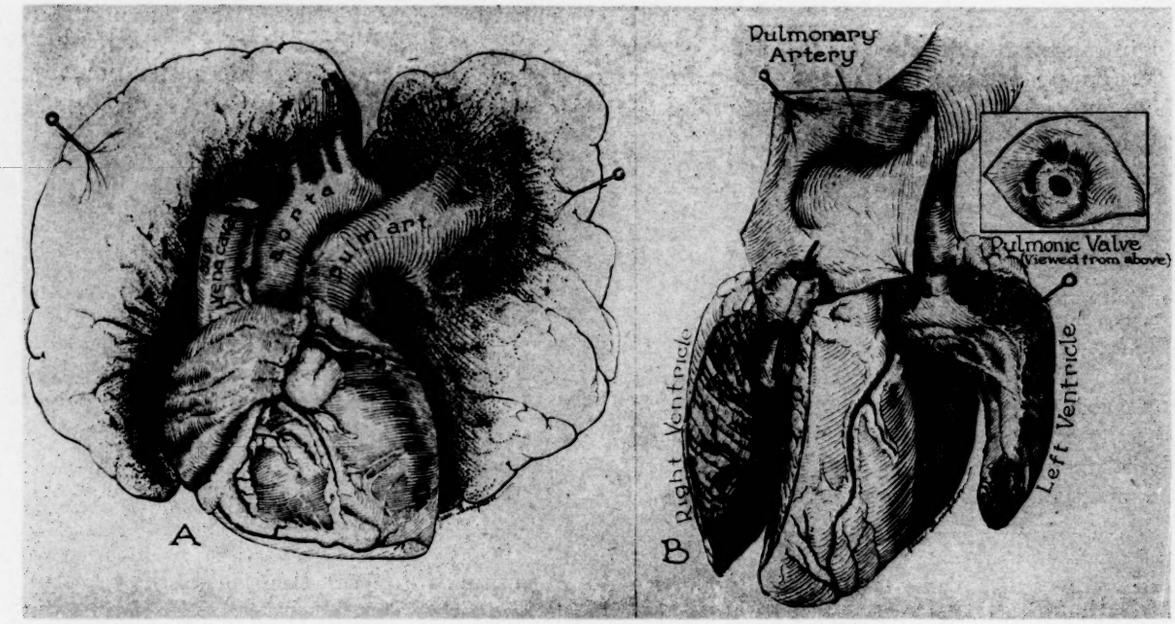


FIG. 2. Drawing of the heart and great vessels in Case I. A, anterior view of the heart and lungs showing position of the heart and the dilated pulmonary artery. B, section of the heart showing the thickness of the two ventricles and the dilated pulmonary artery. *Inset* upper right hand corner, pulmonary valve seen from above.

marked enlargement of the pulmonary artery and its left branch. (Fig. 1A.) In the left anterior oblique position the apex of the heart showed a notch, suggesting the interventricular groove and thus showing that it was formed mostly by the right ventricle. (Fig. 1B, arrow.)

The patient had repeated attacks of more severe cyanosis with dyspnea. In one of these attacks, on the fourth day after admission, he became irrational and then lapsed into a coma and died.

At autopsy it was revealed that the head, mucosae and upper chest were deep blue. The fingers were moderately clubbed and the nail beds blue. The toes were not clubbed. There was no palpable subcutaneous edema. The serosal surfaces of the abdominal, thoracic and pericardial cavities were normal and there was no fluid in the cavities. The liver edge did not descend below the costal margin.

The heart lay more nearly transversely in the thorax than normally. The entire visible surface from the anterior view was formed by the right ventricle and atrium. (Fig. 2A.) The right atrium was markedly dilated. The right ventricle was dilated and markedly hypertrophied. Its wall measured 18 mm. thick in the conus region. The foramen ovale was covered by the usual endocardial flap, the left margin of which was free so that a round probe 1.5 cm. in diameter could be passed through it. The tricuspid ring measured 12.9 cm. An interrupted row of small, pale vegetations about 1 mm. wide was found along the line of closure of the tricuspid leaflets and there was an appreciable thickening of the leaflets and several chordae tendineae. The mural endocardium of both the atrium and the ventricle was smooth and thin. The pulmonic valve was extremely stenosed. (Fig. 2B.) It was composed of a dome-shaped, stiff, white membrane with a tiny, round orifice between 2 and 3 mm. in diameter. A continuous row of tiny, pink, translucent vegetations lined the free margin of this orifice. There were no distinct separate cusps but four distinct thin commissures joined the membrane to the base of the pulmonary artery. The pulmonic valve ring had a circumference of 5 cm. The pulmonary artery dilated gradually from the valve ring to the bifurcation and its wall became much thinner in the distal end but the intima was smooth and normal. The dilatation extended into the left main branch of the pulmonary artery giving rise to an aneurysmal sac in the left hilar region corresponding to the shadow in the x-ray film. (Fig. 1A.) The wall of this dilated artery was thin and the intima perfectly smooth but for the wrinkles produced by its collapse when emptied. The vessel was perfectly elastic. There was only a small plaque

in the intima of the artery 2.4 cm. distal to its origin marking the former orifice of the ductus arteriosus. The dilatation did not extend into the secondary branches of the pulmonary artery. The right main branch of the pulmonary artery was about one-half the diameter of the left and appeared normal.

The pulmonary veins emptied normally into the left atrium. There was no enlargement of the left atrium or ventricle. The mitral valve appeared normal and its ring measured 8.7 cm. The left ventricle was 10 mm. thick. The mural endocardium was smooth; the aortic valve appeared normal. Its ring measured 7.2 cm. The myocardium had a normal color and appearance except for a small white scar near the apex of the left ventricle. The coronary arteries were free of sclerosis.

The ascending aorta contained a few very thin yellow intimal plaques. A small yellowish-white plaque in the arch marked the former orifice of the ductus arteriosus. A thin, short ligamentum arteriosum, without a lumen, joined this to the left pulmonary artery. The left bronchial artery arose just distal to the arch of the aorta by an unusually large orifice about 2 mm. wide. The vessel was tortuous and a little larger than normal. In order to trace its course the lungs, heart and aorta were removed *en bloc*. A thick suspension of bismuth oxychloride was injected under a pressure of 130 mm. of mercury into the cannulated artery. This suspension, which ordinarily does not pass the arterioles, poured profusely out of the left pulmonary artery indicating unusually wide anastomoses.

The lungs weighed 670 Gm. together. They were pale, soft and crepitant. The liver weighed 1,375 Gm. and its cut surface showed patchy lobular atrophy and hyperemia. The spleen weighed 255 Gm. and was very firm and almost black. The kidneys weighed 340 Gm. together and were similarly very dark and hyperemic. The organs and tissues generally were all suffused. The bone marrow of ribs, sternum, vertebra and femur were uniformly deep red.

Histologic examination showed that the myocardium contained distinct perivascular cuffs of fibrosis, particularly in the interventricular septum. The myocardial fibers of the right ventricle were thickened. The small scar in the left ventricle was composed of old hyalinized collagenous tissue containing many small thick-walled vessels. The coronary arteries generally were delicate. The pulmonic valve was markedly thickened, due principally to increased thickness of the central stratum which was hyalinized and contained a fine, dust-like basophilic deposit of calcification. Tiny thin-walled vessels extended through this layer almost to the free margin of the valve which was surmounted by a small, acidophilic, hyaline, amorphous deposit that contained no cells. The tricuspid valve also contained a number of small, thin-walled vessels and small, amorphous, acidophilic deposits on its line of closure which were virtually acellular. The mitral valve was moderately vascularized but showed no vegetations. The aortic valve was normal. The aorta contained only very small intimal plaques composed principally of foam cells. The pulmonary artery had a normal structure except that the thickness of the wall in the distal dilated portion was reduced to about one-half that of the proximal portion. A cross section of the ligamentum arteriosum showed a complete obliteration of the lumen by hyalinized fibrous and elastic tissue. The lungs were normal except for the presence of occasional eccentric thickenings of the walls of small arteries. (100 to 200 micra diameter.) The injected radiopaque material could be identified in small bronchial arteries, pulmonary arteries and occasional very dilated capillary vessels in the peribronchial connective tissue and surrounding alveolar walls. There was marked passive congestion of the other viscera.

Comment. This patient presented the fully developed picture of congenital heart disease with persistent cyanosis. Secondary polycythemia and clubbing of the fingers and toes offered objective evidence of chronic anoxia. Cyanosis developed rather late in life and did not interfere with a moderately active life until the age of thirty-four. At that time intensification of dyspnea and cyanosis started the patient on a gradual downhill course, with death at the age of thirty-nine resulting from severe anoxia. From the diagnostic standpoint the confusing clinical factor was the radiologic appearance of the widely dilated pulmonary artery, the left branch of which was at one time mistaken for a lung tumor.

Pathologically, there was a high degree of stenosis of the pulmonary valve with a

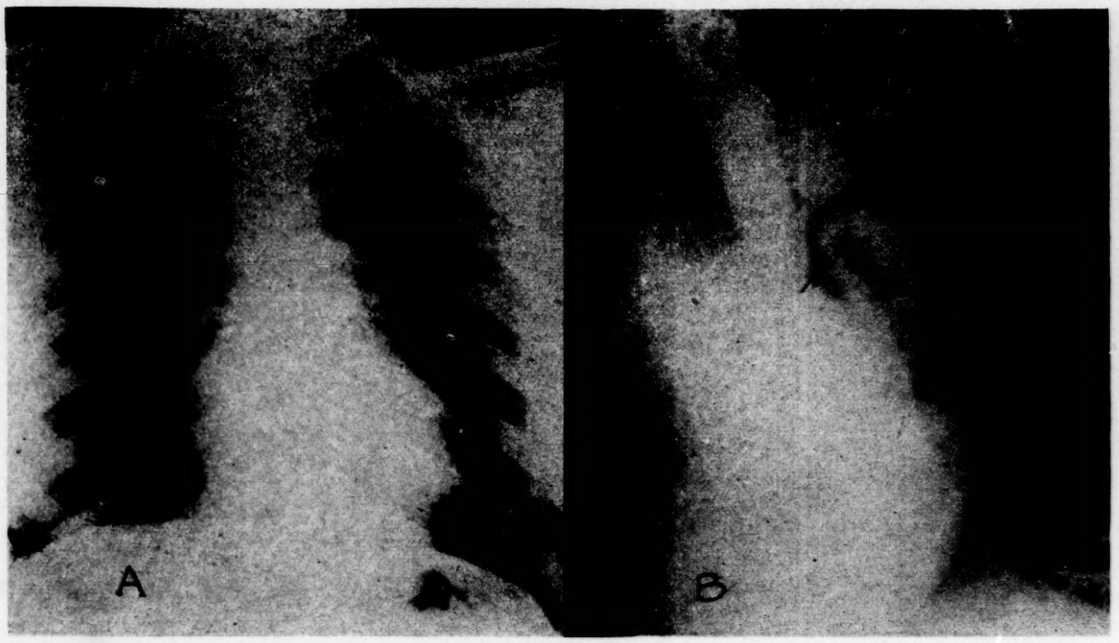


FIG. 3. Roentgenograms in Case II. A, postero-anterior view of the heart showing a normal-sized heart with a hypoplastic aorta and prominent pulmonary artery. B, diodrast-cardiogram interpreted as showing the contrast medium filling the superior vena cava, the right auricle and a stream of the contrast material reaching the left auricle through a patent foramen ovale (arrow). (Courtesy of Dr. Earl Miller, Department of Radiology, University of California Hospital.)

peculiar cup-shaped deformity of the fused valves, a dilatation of the pulmonary artery and wide patency of the foramen ovale. There was also evidence of large collateral circulation to the pulmonary branches from the bronchial artery. The right ventricle was severely hypertrophied, but there was no evidence of chronic congestive failure.

CASE II. L. C., a twenty-five year old divorced white woman, entered San Francisco Hospital on January 10, 1947, complaining of dizziness and episodes of fainting on exertion.

She had first been seen in this hospital in August, 1943 because of salpingo-oophoritis, and at that time was also thought to have congenital heart disease and rheumatic heart disease with mitral stenosis and pulmonary insufficiency. She gave a history of having rheumatic fever at four and since then she has had episodes of exertional dyspnea, dizziness and occasional syncope which she attributed to rheumatic heart disease. She was not cyanotic but was found to have clubbing of the fingers which she thought she had had for many years. Her hemoglobin was 15 Gm. and the red blood count was 4.35 million.

She was next seen at the University of California Hospital in November, 1946 because of dyspnea, weakness, dizziness and fainting on exertion. She stated at that time that these symptoms had occurred off and on during her whole life but were occurring with increasing frequency during the previous three months. She was found to have moderate cyanosis and marked clubbing of her fingers and toes. The heart was slightly enlarged to the left, and there was a moderately loud systolic murmur over the entire precordium, best heard in the third intercostal space at the left sternal border which was also radiating to the axilla and the left scapula. The second sound was louder at the pulmonic area than at the aortic. The liver was slightly enlarged and somewhat tender. A blood count revealed a hemoglobin of 16.6 Gm. and 6.5 million erythrocytes. An electrocardiogram showed marked right axis deviation with inverted T waves in leads II, III, and IV_F and a prominent tall P_2. (Fig. 4A.) Roentgen examination of the chest revealed the heart to be within normal limits of size with a prominent shadow of the pulmonary artery. (Fig. 3A.) Diodrast cardiography was interpreted as showing an interauricular communication with a right to left flow of the contrast material (Fig.

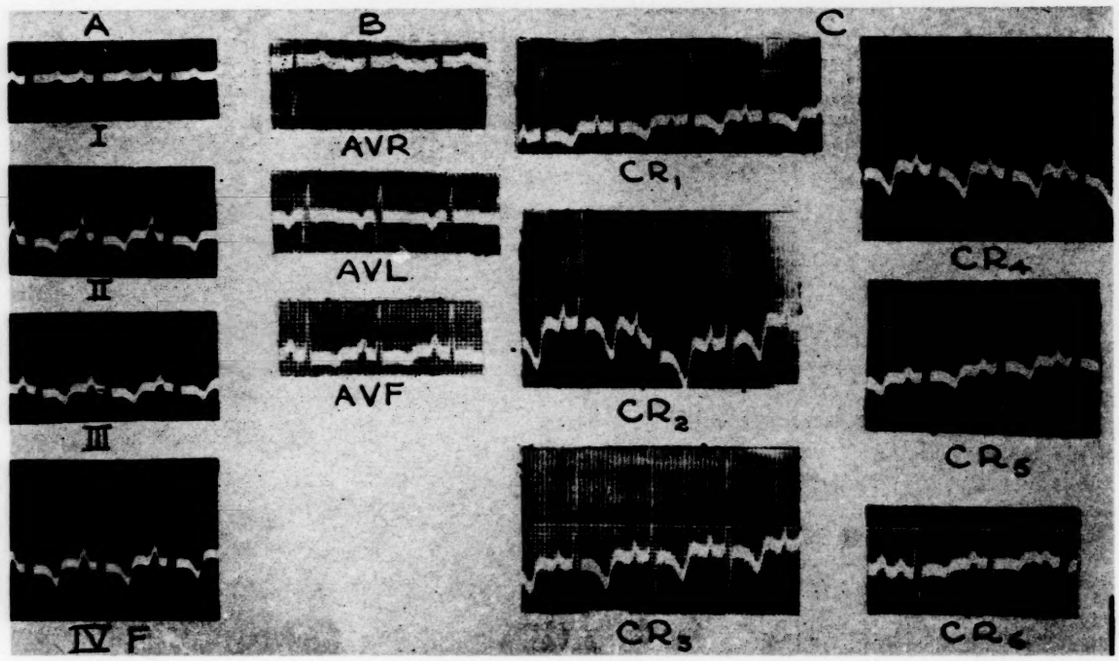


FIG. 4. Electrocardiograms in Case II. A, four-lead electrocardiogram showing the patterns of right ventricular hypertrophy. B, unipolar extremity leads. C, precordial leads, both confirming the diagnosis of right ventricular hypertrophy.

3B), large pulmonary arteries and hypoplasia of the aorta. Diagnosis of congenital heart disease with an interauricular septal defect and hypoplasia of the aorta was made.

Following discharge from the University of California Hospital, the patient continued to have dyspnea, dizziness and fainting episodes with increasing frequency and finally, in January, 1947, reentered the San Francisco Hospital. At that time the cyanosis was found to be severe and she would faint if allowed to stand for a few minutes or upon any exertion. Her blood pressure was 120/90. There was a widely split first heart sound at the apex and a moderately loud, harsh systolic murmur transmitted to the axilla. Another systolic murmur was heard at the second and third left intercostal space. Second sound was present at the pulmonic area. The liver was slightly enlarged; there was no edema. Laboratory studies were essentially negative except for a hemoglobin of 15.9 Gm. and erythrocytes numbering 11 million. The hematocrit reading was 60. An electrocardiogram showed the pattern of right ventricular hypertrophy, essentially as shown in Figure 4A, with additional confirmation of this diagnosis by unipolar extremity leads and leads $V_1 - V_6$. (Fig. 4B.)

Her course in the hospital was slowly but progressively downhill. She became more markedly cyanotic and dyspneic and fainted on such mild exertion as turning in bed. During the last ten days she developed a low grade fever which was unexplained and she expired on February 6, 1947.

Autopsy was performed seventy-six hours after death by one of us (R. H.) and was limited to examination of the thoracic cavity because of the terms under which consent was granted.

The body was that of a well developed, well nourished, white female measuring 64 inches in length and appearing to be about the stated age of twenty-five years. The weight was approximately 110 pounds. The body showed no edema, but there was well developed postmortem lividity over its posterior and lateral aspects. There was bilateral clubbing of the fingers and toes.

The right pleural cavity contained 100 cc. of clear, amber-colored fluid, and the left pleural cavity contained 250 cc. of a similar type fluid. The mediastinum was in the midline and small remnants of thymic tissue and fat were present in the superior mediastinum. The pericardial sac contained 50 cc. of clear, amber-colored fluid.

The heart was transverse in position with the anterior surface made up of dilated right auricle

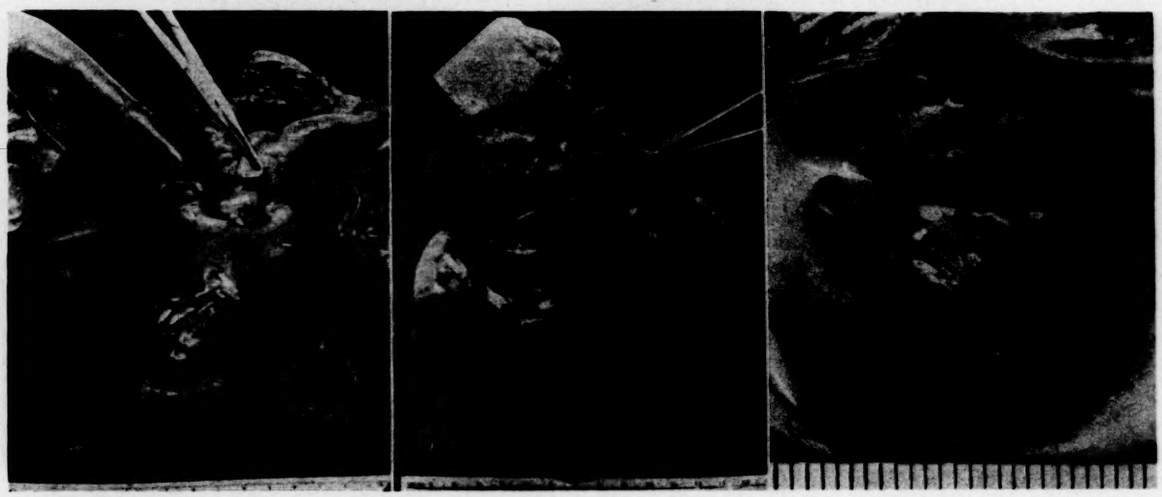


FIG. 5. Photograph of the heart in Case II. A, view of the heart, the stenosed pulmonary valve and the thin-walled, dilated pulmonary artery. B, view of the hypertrophied right auricle and ventricle and the patent foramen ovale (forceps). C, close-up of the pulmonary valve viewed from above.

and enlarged right ventricle. It weighed 330 Gm. and measured 13 by 10.5 by 7 cm. The wall of the right auricle was thickened and on its outer surface were small, fibrous, granular thickenings of the epicardium. The foramen ovale was patent and allowed passage of one finger through the interauricular septum. On the left auricular side was a well developed, thin, fibrous septum with a crescentic opening measuring 1.5 cm. long. The septum covered the opening sufficiently to have acted as a flap valve preventing the flow of blood from the left auricle to the right auricle whereas flow from the right to the left was possible. The left auricle was small and the wall averaged 2 mm. in thickness. The tricuspid valve admitted three fingers with ease and measured 8.5 cm. in circumference. The valve cusps were thickened and there were small warty, pale, greyish-pink vegetations along the margin of closure near the centers of two of the cusps. Some of the chordae tendineae were quite markedly thickened. The wall of the right ventricle was hypertrophied and varied in thickness from 10 to 15 mm. The pulmonary valve showed a complete fusion of all of the free margins of the cusps so that there was a dome-shaped, fibrous diaphragm with a central opening which measured 2 mm. in length and 1 mm. in width. This was the only opening through the pulmonary valve ring. The margins of the opening were fringed with numerous tiny, beaded, translucent, friable, greyish-pink vegetations. (Fig. 5.) The wall of the pulmonary artery was approximately one-third the usual thickness and the artery was dilated above the valve ring. It measured 2 cm. in diameter just above the valve, and was 3.5 cm. in diameter 2 cm. above the valve ring. In the region of the ductus arteriosus the pulmonary artery was closely approximated to the under surface of the aorta and showed a small dimple in the wall. On the aortic side there was a deeper, funnel-shaped depression which extended obliquely through the wall of the aorta toward the dimple in the pulmonary artery. There was no communication from either side. A large atheromatous plaque was present in the aorta adjacent to the obliterated ductus. The wall of the left ventricle averaged 11 mm. in thickness and the chamber was normal in size. The mitral and aortic valves showed no evidence of disease and were normal in structure. The circumference of the mitral valve was 9 cm. and that of the aortic valve was 6 cm. The aorta was small with a wall of normal thickness. Its circumference was 6 cm. immediately above the aortic ring, 5 cm. 3 cm. above the ring, and 3.9 cm. 6 cm. above the ring. The lower part of the thoracic aorta was 3.5 cm. in circumference. The coronary vessels had a normal distribution and the walls were not thickened.

The right lung weighed 360 Gm. and the left lung weighed 340 Gm. Both lungs were normally aerated and no gross areas of consolidation were present. They were moderately congested but not otherwise unusual upon cut section.

Histologic examination revealed that the myocardial fibers in the right ventricle were

increased in size and were as large as those in the left ventricle. The nuclei were centrally placed and frequently were rectangular in outline. The myofibrils were well preserved but cross striations were indistinct. The majority of the fibers had an increase in the amount of perinuclear pigment, and occasional fibers showed separation of the fibrils. There were occasional small patchy areas of fibrosis between muscle bundles and perivascular fibrosis was also occasionally found. Small foci of lymphocytes and mononuclear cells were present in and adjacent to the fibrous areas. Aschoff bodies were not seen. The cusps of the pulmonary valve were thickened, with the thickest portion midway between the orifice and the attachment, and tapered toward the orifice. The cusps had an increased vascularity with numerous small vessels far out toward the free margin. The thickening was due to the presence of broad hyalin collagenous fibers. The surfaces of the valve were covered with a smooth layer of endothelial cells except at the orifice where the endothelium was interrupted by a proliferation of large, stellate-shaped cells with large hyperchromatic nuclei. These cells showed a slight tendency toward palisading and extended outward for a short distance into masses of fibrin which were adherent to the underlying connective tissue of the cusp. The fibrin was homogeneous and contained very few cells. No bacteria could be demonstrated within the vegetations. The valve cusps attached to the root of the pulmonary artery in a normal manner. The artery above the valve was thin but showed the usual histologic arrangement of elastic fibers. The tricuspid valve was thickened with increases of collagenous connective tissue and blood vessels. Along the margin of closure there was a zone of endothelial ulceration and an adherent fibrinous vegetation similar to those found on the pulmonary valve. The structure of the mitral and aortic valves was normal. Sections through the walls of the aorta and pulmonary artery in the region of the ductus arteriosus showed a short small channel with the lumen obliterated by a completely organized fibrous mass. The aorta had a wall of normal thickness with intact elastic fibers and no evidence of degeneration or inflammation. Sections from several portions of the lungs showed patchy early bronchopneumonia as well as quite pronounced congestion of alveolar capillaries in most regions.

Comment. This patient developed visible cyanosis only a few months before death although clubbing of the fingers and toes was known to have existed for a long time. Cyanosis and polycythemia progressed within a very short time to extreme degrees and the patient died at the age of twenty-five from anoxia. Roentgenologic examination revealed a dilated pulmonary artery and, with the use of diodrast, a defect in the interauricular septum with a right to left blood flow.

Necropsy showed a diaphragm-type stenosis of the pulmonary valve of high degree, a widely patent foramen ovale, marked hypertrophy of the right ventricle and a dilated pulmonary artery. There was evidence suggesting that the ductus arteriosus may have been patent in adult life and obliterated shortly before death. The recent obliteration of the ductus arteriosus may have been the cause of the sudden development and rapid progression of severe cyanosis.

FINDINGS IN CASES TAKEN FROM THE LITERATURE

Maude Abbott's chart of 1,000 cases of congenital heart disease[2] contains twenty-five cases of pulmonary stenosis with intact interventricular septum.[5–26] Sixteen of these had a patent foramen ovale and in nine the foramen ovale was closed. All but two of these cases have been reviewed and an additional twenty-seven similar cases have been collected from the literature.[4,27–40] In order to establish characteristic features for the differential diagnosis of these cases a well documented group of control cases with other congenital lesions and cyanosis has been assembled. This includes twenty-eight cases of proven tetralogy of Fallot[41–62] and thirteen cases of Eisenmenger complex.[3,31,63–71] Since the primary objective of this report is to establish diagnostic criteria for fully developed clinical entities, the control group was limited to autopsied subjects above fifteen years of age and consisted of Abbott's cases supplemented by more recently reported cases.

Cases of pulmonary stenosis* with intact interventricular septum and patent foramen ovale are presented in some detail. (Table I.) The twenty-three cases of pulmonary stenosis with both septa intact and the control group (twenty-eight cases of the tetralogy of Fallot and thirteen cases of the Eisenmenger complex) have been analyzed and their various clinical and pathologic features compared with those of pulmonary stenosis with patent foramen ovale in Tables II to VII. Special care was exercised in the compilation of the tables to avoid error resulting from the comparison of groups containing children as well as adults with control groups consisting of only those above the age of fifteen. Whenever it was thought that the age may have influenced the incidence of various features, cases of pulmonary stenosis with closed interventricular septum were also limited to those over fifteen in order to make all groups comparable.

Table I summarizes clinical and pathologic findings in patients with pulmonary stenosis with patent foramen ovale and includes twenty-seven cases from the literature and two of our own. The similarities between many of these cases justify separation of this syndrome as a clinical entity not only from the tetralogy of Fallot and the Eisenmenger complex, but from pulmonary stenosis with both septa intact as well. Some of the clinical features of pulmonary stenosis with patent foramen ovale are characteristic enough to make this syndrome a clinically recognizable entity. These features can best be emphasized by comparing this group of cases with others having similar congenital lesions.

Cyanosis. The most important single feature in the diagnosis of congenital heart disease is cyanosis. Cyanosis is the dividing line between various groups of lesions. It is shown conclusively in Table I that pulmonary stenosis with patent foramen ovale belongs to the cyanotic group of congenital lesions. Table II contrasts the incidence and degree of cyanosis in this syndrome with that in other forms of pulmonary stenosis and in the Eisenmenger complex. The first part of the table shows that pulmonary stenosis with closed foramen ovale is a noncyanotic lesion with rare exceptions. The contrast between these two forms of pulmonary stenosis has been analyzed in relation to the mechanism of cyanosis elsewhere.[72] It may be pointed out here, however, that a critical review of the six cases of pulmonary stenosis with closed foramen ovale and cyanosis[72] reveals that only one of them presented the fully developed picture of chronic cyanosis with secondary polycythemia and clubbing.[29] In this case no detailed description of the foramen ovale is presented and an error cannot be ruled out. In the remaining five cases the evidence of persistent cyanosis was not very convincing. On the other hand, in the single case of pulmonary stenosis with patency of the foramen ovale in an adult without cyanosis the foramen was very small. Therefore, it appears that cyanosis in pulmonary stenosis with intact interventricular septum depends on the shunt from the right auricle to the left auricle through the patent foramen ovale.

In the second and third parts of Table II pulmonary stenosis with patent foramen ovale is compared with the tetralogy of Fallot and the Eisenmenger complex. There is no basic difference between the first two types in the degree of cyanosis and the age of onset. Severe cyanosis is infrequent in the Eisenmenger syndrome but the age of onset of cyanosis is similar to that in the other types.

Polycythemia and Clubbing. Secondary polycythemia and clubbing of the fingers and toes offer objective evidence of long-standing arterial anoxemia. Table III shows the incidence of these signs in the four types of congenital heart disease under discussion in cases in which the observations were recorded.

Auscultatory Physical Findings. Auscultation of the heart is an important method of

* Pulmonary stenosis is used hereafter to signify pulmonary stenosis with intact interventricular septum as contrasted with the tetralogy of Fallot.

TABLE I

SUMMARY OF FINDINGS IN TWENTY-NINE CASES OF PULMONARY STENOSIS WITH PATENT FORAMEN OVALE, ARRANGED IN ORDER OF AGE AT TIME OF DEATH

Case No.	Author	Age, Sex	Physical Signs	Cyanosis	Clubbing	Blood Count	Electrocardiogram	X-Ray	Cause of Death	Heart Weight (Gm.)	Pulmonary Stenosis		Foramen Ovale	Pulmonary Artery	Other Features
											Type	Degree			
1.	Currens 1945[4]	3 mo. F	Pulmonic systolic murmur; P_2 diminished	0	0	Normal	.....	.....	Subdural hematoma	...	Stenosis of annulus	1 cm. diameter	Open		
2.	Kossman 1942[18]	4 mo. F	Precordial systolic murmur	+++	....	R.B.C., 7.7 million Hgb., 22 Gm.	.....	Normal heart	Heart failure	...	Diaphragm	Pinpoint	Open	Large	Patent ductus arteriosus
3.	Taussig 1947[31]	7 mo. M	Harsh precordial systolic murmur	+++	....	.....	.....	Pulmonary conus full	Heart failure	...	Fused cusps forming dome	1.5 mm. diameter	Patent	Moderately dilated	
4.	Barlow 1878[16]	4 yr. F	Pulmonic systolic murmur	+	+	.....	.....	.....	Measles	...	Funnel-shaped dome	Small slit	Admits goose quill	Dilated	
5.	Andrew 1864[13]	6 yr. M	Loud pulmonic systolic murmur	+	0	.....	.....	.....	Erysipelas	...	Cup-shaped	Minute aperture	Widely open	.....	Ductus arteriosus admits small probe; bicuspid aortic valve
6.	Currens 1945[4]	11 yr. M	Loud murmur, thrill at base; P_2 diminished	+	....	.....	.....	.....	Cerebral abscess	340	Fused valves	Buttonhole 9 mm. long	Open 1.1 by 0.3 cm.		
7.	Cassell 1891[16]	11 yr. F	Pulmonic and apical systolic murmurs, P_2 diminished	Since birth +++	++	.....	.....	.....	Anoxia	...	Cup-like	Round central opening	Open	.....	Ductus arteriosu closed
8.	Saundby 1879[23]	11 yr. M	Systolic and diastolic murmur at base	0	....	.....	.....	.....	Heart failure	...	Adherent valves form ring	Round 9/16 inch	15/16 inch	.....	Tiny pulmonic vegetations
9.	Tuley 1917[28]	13 yr. M	Systolic and diastolic murmur and thrill at base	Since 9 yr. +	+	.....	.....	.....	Subacute bacterial endocarditis	350	Fused rings	Admits small probe	5 mm. diameter	Markedly dilated	Massive pulmonic vegetations
10.	Abbott 1923[12]	14 yr. F	Moderately loud pulmonic systolic murmur; P_2 diminished	Progressive since 9 yr. +++	++	R.B.C., 7.6 million Hgb; 120 per cent	Right axis deviation, tall P waves	Enlarged heart, fullness of pulmonary artery	Anoxia	...	Fused valves form membrane	Circular opening 2 mm. diameter	Admits pencil	.....	Tiny pulmonic vegetations
11.	Gaines 1913[18]	15 yr. F	Loud pulmonic systolic murmur	0	....	.....	.....	.....	Tuberculosis	...	Ostium stenosed	8 mm. diameter	2 mm. perforation	Small	
12.	Currens 1945[4]	17 yr. M	Moderately loud pulmonic systolic murmur; P_2 diminished	Mild since 4, +++ since 15	++	R.B.C., 8.7 million Hgb., 22 Gm.	Right axis deviation, tall P waves	Enlarged heart and pulmonary artery	Anoxia	380	Fused valves	Oval 6 mm. diameter	1 cm. diameter	Moderately dilated	
13.	Vandam 1947[30]	17 yr. F	Loud pulmonic systolic murmur and thrill	Onset at 2, progressive to +++	++	R.B.C., 10.1 million Hgb., 21 Gm.	Right ventricular hypertrophy	Prominent pulmonary artery nonpulsating	Operation (anesthesia?)	...	Fused cusps conelike	2 mm. diameter	Widely patent	Slightly dilated	Large bronchial arteries
14.	Wilks 1858[26]	18 yr. F	Pulmonic systolic murmur	++	....	.....	.....	.....	Tuberculosis	...	Funnel shaped diaphragm	4 mm. diameter	2.5 cm. diameter	.....	Tiny pulmonic vegetations
15.	Peacock 1848[22]	20 yr. M	Systolic murmur and thrill, left sternal border; loud P_2	++	+	.....	.....	.....	Tuberculosis	360	Diaphragm	Triangle admits pencil	6 mm. diameter		

TABLE 1 (*Continued*)

Case No.	Author	Age, Sex	Physical Signs	Cyanosis	Clubbing	Blood Count	Electrocardiogram	X-Ray	Cause of Death	Heart Weight (Gm.)	Pulmonary Stenosis		Foramen Ovale	Pulmonary Artery	Other Features
											Type	Degree			
16.	Auerbach 1947[29]	20 yr. M	Pulmonic systolic murmur	since 17 yr. +++	++	R.B.C., 7.0 million Hgb., 21 Gm.	Right bundle branch block, tall P waves	Normal heart, enlarged pulmonary artery	Pneumonia and heart failure	520	Diaphragm	2 mm.	1.2 by 0.8 cm.	Normal	Slight tricuspid stenosis
17.	Paul 1871[27]	20 yr. M	Pulmonic systolic murmur and thrill, diastolic murmur	since 7 yr., severe since 14 +++		.....	.....	.....	Tuberculosis	...	Funnel-shaped	Triangle 5 mm.	Widely patent	Aneurysmal dilatation	
18.	Scremini 1925[24]	21 yr. F	Pulmonic systolic murmur and thrill	++	++	R.B.C., 6.6 million Hgb., 100 per cent	.....	.....	Pulmonary infarct	...	Cup-shaped membrane	Perforation 4 mm. diameter	9 mm. diameter	Dilated	
19.	Lafitte 1892[19]	21 yr. F	Pulmonic systolic murmur and thrill	0	....	.....	.....	.....	Tuberculosis	470	Subvalvular diaphragm	Triangle 3 mm.	4 mm. diameter	.....	Tiny pulmonic vegetations
20.	Niergarth 1889[21]	21 yr. M	.....	since infancy +++	....	.....	.....	.....	Tuberculosis	215	Funnel-shaped diaphragm	5 mm. diameter	1 cm. diameter	Small	
21.	Currens 1945[4]	22 yr. F	Loud systolic murmur, left sternal border	++ terminally +++	....	.....	.....	.....	Heart failure	630	Fused valves	.....	5 mm. by 5 mm.		
22.	McPhedran 1924[2]	23 yr. F	Soft apical systolic murmur, P_2 diminished	since birth; +++ since 16	....	R.B.C., 12.5 million Hgb., 140 per cent	.....	.....	Subacute bacterial endocarditis	390	Funnel-shaped	3 mm. diameter	8 mm. diameter	.....	Endocarditis tricuspid valve, tiny pulmonic vegetations
23.	Finlay 1878[17]	23 yr. F	Loud pulmonic systolic murmur and thrill	since birth +++	++	.....	.....	.....	Heart failure	...	Fused valves	5 mm. diameter	1.0 by 1.3 cm.	.....	Ductus arteriosus closed
24.	Our Case 11	25 yr. F	Loud systolic murmur, left sternal border; P_2, A_2 at apex	++ since 24 yr.	since 21 ++	R.B.C., 11.0 million Hgb., 16.6 Gm.	Right axis deviation, tall P waves	Dilated pulmonary artery	Anoxia	330	Funnel-shaped diaphragm	2 mm. diameter	Large	Dilated	Ductus arteriosus closed, tiny pulmonic vegetations
25.	Currens 1945[4]	30 yr. M	Systolic murmur left sternal border; loud P_2	++ since childhood	....	R.B.C., 5.8 million Hgb., 90 per cent	.....	.....	Lobar pneumonia	430	Fibrous fusion of valves	Admits pencil	6 mm. diameter	Intraventricular pulmonic branches good size	Tricuspid valve slightly thickened, nodular
26.	Frerichs 1853[27]	34 yr. M	Diastolic murmur left sternal border; P_2 heard	++	....	.....	.....	.....	Tuberculosis	...	Funnel-shaped diaphragm	Pinpoint	Open	Large	
27.	Our Case 1	39 yr M	Mild systolic murmur, apex	onset at 18, progressive to +++	++	R.B.C., 9.4 million Hgb., 188 per cent	Right axis deviation, tall P waves	Dilated pulmonary artery	Anoxia	535	Funnel-shaped diaphragm	5 mm.	2.1 cm.	Dilated aneurysm-like	Ductus arteriosus closed, tiny pulmonic vegetations, large bronchial arteries
28.	Ballet 1880[14]	47 yr. F	Precordial murmur and thrill	++	....	.....	.....	.....	Cerebral abscess	...	Funnel-shaped diaphragm	Central hole 5 mm. diameter	Open		
29.	Paul 1871[27]	57 yr. F	Precordial murmur and thrill, P_2 audible	mild since childhood; ++ after 47	....	.....	.....	.....	Cerebral abscess	360	Funnel-shaped diaphragm	5 mm. diameter	Patent		

TABLE II

INCIDENCE, ONSET AND DEGREE OF CYANOSIS IN VARIOUS FORMS OF PULMONARY STENOSIS AND IN THE EISENMENGER COMPLEX

I. Cyanosis in pulmonary stenosis with and without patency of the foramen ovale

	Pulmonary Stenosis with Patent Foramen Ovale	Pulmonary Stenosis with Closed Foramen Ovale
Cyanotic patients		
total number	25	6
over the age of 15	17	3
Non-cyanotic patients		
total number	4	17
over the age of 15	1	13

II. Onset of cyanosis in pulmonary stenosis with patent foramen ovale in the tetralogy of Fallot and in the Eisenmenger complex

Age of Onset	Pulmonary Stenosis with Patent Foramen Ovale	Tetralogy of Fallot	Eisenmenger Complex
0–5	10	9	4
6–10	3	5	2
11–15	..	..	1
over 16	4	4	4
information not available	8	10	2

III. Degree of cyanosis during terminal illness

	Pulmonary Stenosis with Patent Foramen Ovale (Patients over 15)	Tetralogy of Fallot	Eisenmenger Complex
None	1	1	0
Mild	0	2	3
Moderate	8	5	8
Severe	9	17	1
Total	18	25	12

identifying and differentiating various congenital cardiac lesions. It is fully realized that compilation of data from such a heterogeneous group of cases reported by various authors at different periods can only be considered approximate, especially since this is an entirely subjective method of examination. The intensity of the murmurs and their transmission were not commented upon in a sufficient number of cases to warrant inclusion in the discussion. The location of the points of maximum intensity of the murmurs is presented usually as described by the authors, except that murmurs recorded as best heard in the second and third intercostal space at the left sternal border were consolidated with those described as located in the pulmonic area, and murmurs best heard in the third and fourth, or the fourth and fifth intercostal spaces were grouped together as lower left sternal border. Many murmurs were recorded as precordial without better specification and are presented here as such. In order to bring out better the differences in location of the murmurs those with specified location of the maximum intensity were then divided into two groups: (1) those over the upper part and (2) those over the lower part of the cardiac projection of the chest wall. The third intercostal space provided the rough dividing line. No correlation could be found between the location of the murmurs and the type of pulmonary stenosis found at autopsy. The murmurs of valvular and subvalvular stenosis were not distinguishable.

Diastolic murmurs were all described as early diastolic, located to the left of the sternum, except for two cases in which a mitral type of rumbling apical murmur was recorded. It was noted that of the five early diastolic murmurs in the tetralogy of Fallot three subjects were found to have bicuspid pulmonary valves.

In a few cases description of physical findings included comments on the intensity of the second sound at the second left intercostal space. The second sound at that area was described as decreased or absent in five cases of pulmonary stenosis with intact in-

terventricular septum and in one case each of the tetralogy of Fallot and the Eisenmenger complex. On the other hand, it was accentuated in four cases of the former group and in five of the control group. It was noted that in four cases of the tetralogy of Fallot with a normal or loud second sound at the left sternal border the pulmonic valves were not grossly abnormal.

TABLE III
INCIDENCE OF POLYCYTHEMIA AND CLUBBING IN PATIENTS OVER THE AGE OF FIFTEEN

	Pulmonary Stenosis with Foramen Ovale Closed	Pulmonary Stenosis with Foramen Ovale Patent	Tetralogy of Fallot	Eisenmenger Complex
Polycythemia				
present	1	8	9	5
absent	6	0	2	0
Clubbing				
present	2	11	17	8
absent	8	2	3	2

Electrocardiographic Findings. Electrocardiograms were reported in twenty-five of the ninety-three cases. Right axis deviation was, as expected, the prominent feature of all four lesions discussed here. It was present in all but one case and that was a case of the Eisenmenger complex. In four cases right bundle branch block was reported, three of which were cases of pulmonary stenosis with intact interventricular septum and one Eisenmenger complex. In none of these four cases were multiple precordial leads or unipolar leads available to permit a finer differential diagnosis between a true conduction defect and ventricular hypertrophy. Prominent, tall P waves were reported in eleven cases and were less common in the tetralogy of Fallot than in the other two types of pulmonary stenosis. None were reported in the Eisenmenger complex.

Roentgenologic Findings. It is rather difficult to compare the x-ray appearance in a group of patients with so many factors affecting the size, shape and position of the cardiac shadow. However, a review of the data revealed that the most striking feature was the appearance of the pulmonary artery, regardless of the size and shape of the ventricular shadow. Table v shows the contract between the x-ray appearance of cases of pulmonary stenosis with and without patency of the foramen ovale and of the tetralogy of Fallot. All patients with pulmonary stenosis, with the exception of one infant, had evidence of dilatation of the pulmonary artery while in the tetralogy of Fallot the pulmonary artery was small in ten cases, questionably enlarged in one case and in one other the cardiac shadow appeared normal. In most cases of pulmonary stenosis the cardiac shadow was not much enlarged so that the two films shown in Figures 1A and 3A can be accepted as representing typical examples of the x-ray ap-

TABLE IV
CARDIAC MURMURS IN VARIOUS FORMS OF PULMONARY STENOSIS AND THE EISENMENGER COMPLEX

	Pulmonary Stenosis with Foramen Ovale Closed	Pulmonary Stenosis with Foramen Ovale Patent	Tetralogy of Fallot	Eisenmenger Complex
Systolic murmurs				
1. Precordial	2	4	1	1
2. In upper half of cardiac projection	15	20	7	3
Pulmonic	11	15	5	3
Area base of the heart	4	5	2	0
3. In lower half of cardiac projection	5	3	13	7
Lower left sternal border	4	1	12	3
Apical area	1	2	1	4
Diastolic murmurs	6	4	5	6
Total: information available	22	28	21	11

pearance of pulmonary stenosis as judged from the fifteen autopsied cases in which x-ray examinations were reported. In the tetralogy of Fallot, too, the heart was most frequently normal in size. "Sabot"-shaped elevation of the cardiac apex was recorded

TABLE V
ROENTGENOLOGIC SIZE OF THE PULMONARY ARTERY AND BRANCHES

	Pulmonary Stenosis with Closed Foramen Ovale	Pulmonary Stenosis with Patent Foramen Ovale	Tetralogy of Fallot	Eisenmenger Complex
Prominent pulmonary artery	7	7	1 (?)	5
Small pulmonary artery	0	0	10	0
Pulmonary artery not remarkable	0	1	1	0

in some, but not in all cases. In one case there was a right-sided aortic arch. The characteristic deep concavity of the left cardiac border was present even in those with cardiac enlargement, notably in the remarkable case of Volini and Flaxman,[59] in which the cardiac shadow occupied 80 to 90 per cent of the transverse diameter of the chest and the heart weighed 750 Gm. In the Eisenmenger syndrome the six patients with a record of radiologic examination showed a very characteristic appearance in that the pulmonary artery was very prominent, there was a very marked dilatation of the hilar shadows and the lung fields were intensely congested. Fluoroscopic examination reported in cases of the Eisenmenger complex invariably revealed prominent pulsations of the hilar shadows. In contrast the dilated pulmonary arteries in pulmonary stenosis with intact interventricular septum were usually described as showing absent or slight pulsations.

Course and Prognosis. In spite of the relatively small number of cases analyzed a certain amount of useful information concerning the prognosis of the various lesions can be obtained by comparing the ages attained by the patients and the cause of

TABLE VI
PROGNOSIS OF THE FOUR TYPES OF CONGENITAL HEART DISEASE

I. Age at death of patients who survived fifteen years of life

	Pulmonary Stenosis with Closed Foramen Ovale	Pulmonary Stenosis with Patent Foramen Ovale	Tetralogy of Fallot	Eisenmenger Complex
15–20	2	6	12	0
21–30	6	8	12	4
31–40	4	2	2	5
Over 41	5	3	2	4

II. Causes of death in these patients

Heart failure	3	3	3	9
Anoxia	1	2	2	0
Bacterial endocarditis	6	1	8	3
Pulmonary tuberculosis	1	7	5	0
Cerebral abscess	0	3	3	1
Other causes	5	3	3	0

death. This is shown in Table VI. Pulmonary stenosis with closed septa and the Eisenmenger complex appear to have a somewhat better prognosis than pulmonary stenosis with patent foramen ovale and the tetralogy of Fallot.

Pathologic Features. The great majority of examples of pulmonary stenosis with intact interventricular septum show strikingly similar anatomic deformities. Of the fifty-one cases forty-three were due to fusion of the cusps. In thirty-two of these the fusion was complete so that a dome-shaped or conical membrane with a small central opening resulted. Sometimes the commissures could be distinguished even when there were no separate cusps as in the two

cases described in this report. In Table VII the types of stenosis are compared in the tetralogy of Fallot and in the two classes of pulmonary stenosis with intact interventricular septum. Valvular fusion occurred in all three classes but it was the nearly exclusive form of stenosis only in the cases with patent foramen ovale and intact interventricular septum. The diaphragm was relatively thin and delicate in some of the youngest subjects but it was thick and rigid in the older patients such as the two reported herein. Histologic examination of the valves was rarely reported except in the presence of bacterial endocarditis. Tiny bland vegetations were often observed on the free margins of the valve orifice. Thickening and mild deformities of the tricuspid valve were frequently noted. The frequent presence of dilatation of the pulmonary artery in those with intact interventricular septum is recorded in the second part of Table VII. The third and fourth parts of the table show that dilatation of the pulmonary artery is directly related to the degree and location of the stenosis.

It is customary to assume that these cases of pulmonary valvular stenosis are congenital. Typical examples have been observed at autopsy in subjects only a few months old and symptoms and signs have been present since birth in many instances. It would be difficult to prove the congenital origin in many cases in adults in whom symptoms appeared late and in whom fibrous thickening and vascularization of the valves so closely resembled the results of rheumatic disease. There are too few reports of careful histologic studies of the heart to provide a basis for generalization on this point. Whatever the pathogenesis of the valvular lesion, the circulatory effects and clinical results would be expected to be the same in all essential respects.

COMMENTS

It appears from the evidence presented that pulmonary stenosis with patency of the foramen ovale is a distinctive entity. Clinically, it is a cyanotic disease and thereby differs from pulmonary stenosis with closed foramen ovale. This is a fundamental difference which justifies very strict separation of these two conditions which are so often grouped together as "pulmonary stenosis with closed interventricular septum." The striking contrast is best illustrated in adult

TABLE VII

PATHOLOGIC FINDINGS IN VARIOUS TYPES OF PULMONARY STENOSIS

I. Type of pulmonary stenosis

	Pulmonary Stenosis with Closed Foramen Ovale	Pulmonary Stenosis with Patent Foramen Ovale	Tetralogy of Fallot
Valvular fusion, diaphragm type	9	23	2
Valvular fusion, partial	6	5	8
Hypoplasia, pulmonary artery	0	0	8
Subvalvular membrane	2	1	8
Conus separate chamber	5	0	1
Total	29	29	20

II. Size of pulmonary artery

Small	1	3	9
Normal	2	1	5
Dilated	6	12	5

III. Relation of the size of pulmonary artery to the type of stenosis

	Valvular Stenosis	Subvalvular Stenosis
Small pulmonary artery	8	4
Dilated pulmonary artery	22	1

IV. Relation of the size of pulmonary artery to the degree of stenosis

	Severe Stenosis	Moderate Stenosis	Mild Stenosis
Small pulmonary artery	0	5	3
Dilated pulmonary artery	12	7	2

patients who, with the same degree and position of pulmonary stenosis, with similar incidence of marked right ventricular hypertrophy and of cardiac failure, develop chronic cyanosis with secondary polycythemia only in the presence of a patent foramen ovale. The cyanosis can only be interpreted as indicative of a large venous-arterial shunt through the foramen ovale. The existence of a right to left shunt has been demonstrated in one of our patients by angiocardiography and in another reported case by cardiac catheterization.[30] That such a course of blood flow is compatible with cardiodynamics even in the absence of right ventricular failure and tricuspid insufficiency has been discussed elsewhere in a study of cyanosis.[72]

In pulmonary stenosis with closed foramen ovale there is no demonstrated cause of chronic cyanosis. Maude Abbott states that in these cases cyanosis is entirely due to capillary stasis but this explanation does not appear very likely. No direct evidence of capillary stasis has ever been presented in pulmonary stenosis without cardiac failure nor have alterations in the velocity and volume of the circulation and in venous pressure been demonstrated. An important argument against such a view is the absence of cyanosis in patients with most marked pulmonary stenosis and cardiac hypertrophy in this series, unless the foramen ovale was patent. A critical review of patients with closed foramen ovale shows that in the few considered cyanotic the evidence is unconvincing. It is not unreasonable to suspect one of three possibilities: (1) cyanosis developed with heart failure and therefore was not different from terminal cyanosis of other cardiac patients, (2) a patent foramen ovale may have been overlooked at autopsy and (3) fetal passages permitting right to left flow may have existed in the past but closed before death. In spite of the fact that Abbott,[2] Currens, Kinney and White,[4] Taussig[31] and others have pointed to the possible rôle of the foramen ovale as a path for an intracardiac shunt this has not been sufficiently emphasized, and the importance of the open foramen ovale in right-sided cardiac lesions is not generally appreciated.

Cyanosis in pulmonary stenosis with patent foramen ovale varies in intensity and may occasionally be absent. In this respect it is not different from the tetralogy of Fallot and the Eisenmenger complex. With any cyanotic lesion, patients may present the picture of morbus ceruleus from birth or may show intermittent cyanosis, late onset of cyanosis or gradual intensification of cyanosis. Pulmonary stenosis with patent foramen ovale occupies an intermediate place between the tetralogy of Fallot, the most severely cyanotic lesion and the Eisenmenger complex, the least cyanotic of the three. It is doubtful, however, whether the degree or time of onset of cyanosis can be used to differentiate these three lesions.

There are no physical signs pathognomonic of pulmonary stenosis. There are, however, important differences between pulmonary stenosis on one hand and the tetralogy of Fallot and the Eisenmenger complex on the other which may be utilized in the diagnosis. In pulmonary stenosis with or without patency of the foramen ovale the systolic murmur is heard in the majority of patients in the pulmonic area whereas with the other two lesions it is more often present along the lower left sternal border. This difference suggests very strongly that the murmur of the tetralogy of Fallot originates in the interventricular septal defect rather than at the site of pulmonary stenosis or, at least, that this represents the more prominent of the two components. As already mentioned no important information could be gained from the description of the intensity of the systolic murmur, its transmission or the presence of thrills. However, the occasional mention of the systolic murmur in the tetralogy of Fallot being conducted to the clavicles and the vessels of the neck suggests the unproven but interesting possibility that such transmission may be a sign of over-riding aorta

and thus evidence against the presence of pulmonary stenosis alone.

Early diastolic murmurs occur most frequently in the Eisenmenger complex at which point they unquestionably represent relative pulmonary insufficiency which is also shown by the marked hilar pulsations. They occur less frequently in the various forms of pulmonary stenosis when they indicate organic pulmonary regurgitation. Because of the anatomic type of the lesion, one might expect an even more frequent occurrence of diastolic murmurs in valvular pulmonary stenosis which accounts for the majority of patients with a closed interventricular septum.

The intensity of the second sound is of limited value in the differential diagnosis. An accentuated second sound along the upper left sternal border most likely indicates absence of pulmonary stenosis or, if the latter is present, subvalvular rather than valvular stenosis. In true valvular stenosis the second sound is often diminished or absent in this area. This relationship, however, is disturbed by the fact that the second heart sound at that location is often transmitted from the aorta as pointed out by Currens et al.[4] and as shown in some of the cases in our series. It was heard in some patients in whom anatomic changes in the valves made their closure appear impossible.

Electrocardiographic examination does not offer any characteristic information about the type of the lesion for all lesions under discussion are associated with right axis deviation. Prominence of the P waves is more common in pulmonary stenosis than in the tetralogy of Fallot and was not noted in the Eisenmenger syndrome. It may be noted that right bundle branch block appeared in three cases of pulmonary stenosis and in none of the tetralogy of Fallot. This suggests that it indicates a high degree of right ventricular hypertrophy rather than an organic defect of the interventricular bundle which should be more likely to occur in septal defects. Some caution has to be exercised therefore in assuming that conduction disturbances are likely to indicate interventricular septal defects.

Roentgenologic examination is by far the most important method in the differential diagnosis of cyanotic congenital lesions. The characteristic x-ray appearance of pulmonary stenosis is due to the poststenotic dilatation of the pulmonary artery in spite of which the lung fields are more radiolucent than normal. These dilated pulmonary arterial shadows show diminished or absent pulsations. This is in contrast to the small size of the pulmonary vessels in the tetralogy of Fallot with a concave "waistline" of the heart, and the more prominent dilatation of the pulmonary conus, artery and branches with intense pulmonary congestion and increased pulsations in the Eisenmenger complex. The characteristic appearance of the sabot-shaped heart of the tetralogy of Fallot is well known. Comparing pulmonary stenosis and the Eisenmenger complex with the better established roentgen configurations of the non-cyanotic congenital lesion, the former resembles that of a patent ductus arteriosus while the latter presents an almost identical x-ray appearance with an atrial septal defect. The striking uniformity of the x-ray pictures presented in Table VI may be a coincidence. From the pathologic analysis of the series one expects to find an occasional case of the tetralogy of Fallot with poststenotic dilatation of the pulmonary artery or a case of pulmonary stenosis with small pulmonary vessels. Occasional exceptions, however, do not weaken the importance of the characteristic x-ray appearance of the various types of pulmonary stenosis, especially since the differences are well explained by the anatomic findings.

The importance of realizing the frequency of the poststenotic dilatation of the pulmonary artery and its effect upon the radiologic appearance of the heart is emphasized by the practical value of the x-ray in selecting patients for the Blalock-Taussig operation. Reliance upon the size of the large pulmonary branches in the selection

of patients for operation[73] would eliminate most of those with pulmonary stenosis with intact interventricular septum. In spite of the very large and dilated pulmonary artery, the appearance of which might make the surgeon hesitant, one may expect pulmonary stenosis with patent foramen ovale to be aided by the operation as much as the tetralogy of Fallot.[72]

TABLE VIII
SUMMARY OF DIFFERENTIAL DIAGNOSIS IN VARIOUS FORMS OF PULMONARY STENOSIS AND THE EISENMENGER COMPLEX

	Pulmonary Stenosis with Closed Foramen Ovale	Pulmonary Stenosis with Patent Foramen Ovale	Tetralogy of Fallot	Eisenmenger Complex
Cyanosis	absent	severe	severe	moderate
Clubbing	absent	marked	marked	moderate
Polycythemia	absent	marked	marked	moderate
Systolic murmurs	pulmonic area	pulmonic area	left sternal border	left sternal border
Diastolic murmurs	occasionally present	occasionally present	occasionally present	common
2d sound pulmonary area	often diminished	often diminished	variable	loud
Electrocardiogram				
Right ventricular hypertrophy	prominent	prominent	prominent	mild
P waves	tall	tall	often tall	not remarkable
Roentgenogram				
Pulmonary artery	enlarged	enlarged	small	markedly enlarged
Hilar shadows	moderate size	moderate size	small	very large, pulsating
Pulmonary congestion	absent	absent	absent	severe

A summary of findings valuable in the differential diagnosis of the three cyanotic lesions and of pulmonary stenosis with closed foramen ovale is presented in Table VIII. Information presented here is based on probability, indicating the features present in the majority of cases analyzed.

The question of how precise an identification of the lesion can be made by the use of newer diagnostic methods, such as angiocardiography and cardiac catheterization, must be left open. These methods are of great value and are becoming established as most important diagnostic procedures in congenital heart disease. Thus far, too few cases have been reported with autopsy confirmation to know whether a demonstration of a lesion by one or both of these methods can be considered definite proof of correctness of the diagnosis.

The question of the prognosis of cyanotic cardiac disease cannot be answered with any degree of accuracy from a small series of cases. It is important, however, to note that more patients die as a result of complications than of cardiac failure. This may be interpreted as showing the ability of the heart to carry the burden of the structural deformities for an amazingly long time. It would follow that symptomatic treatment of the cyanosis, such as the Blalock-Taussig operation, is worth while.

Finally, the relative incidence of the three types of cyanotic cardiac lesion deserves some consideration. It is exceedingly difficult to determine the frequency of various lesions for they are too rare for reliable statistics from any institution and the calculations from the number of cases reported in the literature are misleading. Cases are usually reported only if they present some unusual feature so that rare conditions are reported in greater number than more usual ones. It seems probable that pulmonary stenosis with patent foramen ovale is less common than the tetralogy of Fallot and that it is more common than the Eisenmenger complex. The respective incidences of these three main types of cyanotic congenital heart disease in adult life are unknown.

SUMMARY

Two cases of pulmonary stenosis with intact interventricular septum and patency of the foramen ovale are reported, with an analysis of twenty-seven additional autopsied cases from the literature. This series is compared with the reports of autopsied cases of pulmonary stenosis with both septa closed, of the tetralogy of Fallot and of the Eisenmenger syndrome.

Pulmonary stenosis with patent foramen ovale is characterized by chronic cyanosis, polycythemia and clubbing. In the degree of cyanosis it occupies an intermediate place

between the tetralogy of Fallot and the Eisenmenger syndrome. Pulmonary stenosis with closed septa is essentially a non-cyanotic lesion.

On the basis of cyanosis, cases of pulmonary stenosis with and without patency of the foramen ovale are placed in different classes of congenital heart disease. Otherwise these two diseases are clinically and pathologically very similar and differ from the tetralogy of Fallot in important respects.

The most distinctive feature of pulmonary stenosis with patent foramen ovale is the x-ray appearance of the cardiac shadow which is characterized by a poststenotic dilatation of the pulmonary artery and its branches. This again places the condition in an intermediate position between the small shadows of the pulmonary vessels in the tetralogy of Fallot and the very prominently dilated and congested pulmonary vessels of the Eisenmenger syndrome.

Other clinical features and pathologic findings of this lesion are discussed and evidence is presented that it is a well defined clinical entity with enough distinctive features to make possible diagnosis during life. Next to the tetralogy of Fallot it is the most important congenital cardiac lesion in adults with chronic cyanosis, polycythemia and clubbing.

Pulmonary stenosis with patent foramen ovale represents a conspicuous exception to the rule that cyanotic congenital heart disease with dilated pulmonary arteries is unsuitable for surgical relief.

REFERENCES

1. Blalock, A. and Taussig, H. B.: The surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia. *J. A. M. A.*, 128: 189, 1945.
2. Abbott, M. E. Congenital Heart Disease. In Nelson's Loose Leaf Medicine. Vol. 4, pp. 207-321. New York, 1932. T. Nelson and Sons.
3. Eisenmenger, V. Die angeborene Defekte der Kammerscheidewand des Herzen. *Ztschr. f. klin. Med.*, 32: 1, 1897.
4. Currens, J. H., Kinney, T. D. and White, P. D. Pulmonary stenosis with intact interventricular septum. *Am. Heart J.*, 30: 491, 1945.
5. Abbott, M. E. Congenital Heart Disease. In Nelson's Loose Leaf Medicine. Vol. 4, p. 285, 1932.
6. Bishop, L. F., Jr. and Wallace, S. C. Pulmonary stenosis with bacterial endocarditis in an adult. *Am. Heart J.*, 5: 238, 1929.
7. Clarke, J. J. A case of ulcerative endocarditis associated with stenosis of the conus arteriosus and affecting chiefly the pulmonary valve, with ulceration of the main pulmonary artery. *Tr. Path. Soc. London*, 44: 29, 1893.
8. Hebb, R. G. Stenosis of pulmonary artery; congenital heart disease. *Tr. Path. Soc. London*, 41: 57, 1890.
9. Ogle, J. W. Abnormal condition of the valve at the root of the pulmonary artery with consequent hypertrophy of the parietes of the right ventricle of the heart. *Tr. Path. Soc. London*, 5: 69, 1854.
10. Peacock, T. B. Contraction of the orifice of the pulmonary artery from fusion of the valves. *Tr. Path. Soc. London*, 10: 107, 1859.
11. Peacock, T. B. Case of stenosis of the pulmonary artery from disease of the valves, probably of congenital origin. *Tr. Path. Soc. London*, 30: 258, 1879.
12. Abbott, M. E., Lewis, D. S. and Beattie, W. W.: Differential study of a case of pulmonary stenosis of inflammatory origin and two cases of (a) pulmonary stenosis and (b) pulmonary atresia of developmental origin with associated ventricular septal defect and death from paradoxical cerebral embolism. *Am. J. M. Sc.*, 165: 636, 1923.
13. Andrew, J. Congenital malformation of the pulmonary valve. *Tr. Path. Soc. London*, 16: 81, 1865.
14. Ballet, G. Des abces du cerveau consecutifs a certaines malformations cardiaques. *Arch. gén. de méd.*, 1: 659, 1880.
15. Barlow, T. Congenital heart disease; pulmonary stenosis with dilated pulmonary artery above the stenosis. *Tr. Path. Soc. London*, 30: 272, 1879.
16. Cassell. *Berl. klin. Wchnschr.*, 28: 1221, 1891.
17. Finlay, D. W. Malformation of the heart; stenosis of the pulmonary valve, with dilatation of the pulmonary artery and hypertrophy of the right ventricle; patency of the foramen ovale with cribriform opening in the septum of the auricle. *Tr. Path. Soc. London*, 30: 262, 1879.
18. Gaines, L. M. Stenosis of the pulmonary valve of the heart with tuberculosis of the lungs as a secondary and terminal complication. *Charlotte M. J.*, 67: 228, 1913.
19. Lafitte, A. Rétrécissement infundibulaire de l'artere pulmonaire d'origine congenitale; obliteration incomplete du trou de Botal, absence de cyanose; endocardite vegetante au niveau de rétrécissement. *Bull. Soc. anat. de Paris*, 67: 13, 1892.
20. McPhedran, H. Pulmonary stenosis; patent foramen ovale; acute endocarditis; hemiplegia. *St. Michael's Hosp. M. Bull.* (Toronto), 1: 62, 1924.
21. Niergarth, W. Ein Fall von hochgradiger angeborenen Stenose des Ostium arteriosum dextrum. Tod durch Lungentuberkulose. Munich thesis. 1889.
22. Peacock, T. B. Contraction of the orifice of the pulmonary artery and communication between the cavities of the auricles by the foramen ovale. *Tr. Path. Soc. London*, 1: 200, 1848.
23. Saundby, R. Case of pulmonary stenosis with patent foramen ovale. *Brit. M. J.*, 2: 378, 1877.

24. Scremini, P. and Montes-Pareja, J. Un cas de rétrécissement de l'artere pulmonaire avec propagation du souffle aux vaisseau du cou sans communication inter-ventriculaire. *Arch. d. mal. du coeur*, 18: 304, 1925.
25. Tuley, H. W. and Moore, J. W. Report of a case of congenital endocarditis with vegetative inflammation of the pulmonary artery and valve. *Am. J. Dis. Child.*, 13: 426, 1917.
26. Wilks, S. Malformation of the pulmonary veins. *Tr. Path. Soc. London*, 10: 79, 1859.
27. Paul, C. Du rétrécissement de l'artere pulmonaire. *Bull. Soc. Méd. de Hôp. Paris*, 8: 45, 1871.
28. Kossman, J. I. Congenital atresia and stenosis of great cardiac vessels: aortic atresia, pulmonary stenosis. *Am. J. Dis. Child.*, 64: 872, 1942.
29. Auerbach, S. H. and Harper, H. T., Jr. Congenital pulmonary stenosis with closed interventricular septum. Report of a case associated with patent foramen ovale and slight tricuspid stenosis. *Am. Heart J.*, 34: 131, 1947.
30. Vandam, L. D., Bing, R. J. and Gray, F. D. Physiological studies in congenital heart disease. iv. Measurements of the circulation in five selected cases. *Bull. Johns Hopkins Hosp.*, 81: 192, 1947.
31. Taussig, H. B. Congenital Malformations of the Heart. P. 175. New York, 1947. The Commonwealth Fund.
32. Arnett, J. H. and Long, C. F. A case of congenital stenosis of the pulmonary valve with late onset of cyanosis; death from carcinoma of the pancreas. *Am. J. M. Sc.*, 182: 212, 1931.
33. Eakin, W. W. and Abbott, M. E.: Stenosis of the pulmonary conus at the lower bulbar orifice (conus a separate chamber) and closed interventricular septum with 2 illustrative cases. *Am. J. M. Sc.*, 186: 860, 1933.
34. Blackford, L. M. and Parker, F. P. Pulmonary stenosis with bundle branch block. Report of a case with sound tracings and semiserial studies of the conduction bundle. *Arch. Int. Med.*, 67: 1107, 1941.
35. Hertz, T. Ein Fall von angeborenen Pulmonalstenose ohne anderen Dysplasien and Aplasien mit positivem Denecke'schen Zeichen. *Ztschr. f. Kreislaufforsch.*, 24: 446, 1932.
36. Nabers, L. W. Congenital stenosis of the conus arteriosus with ectasia of the pulmonary artery and bacterial endocarditis of the pulmonary valve. *South. M. J.*, 21: 582, 1928.
37. Leitmann, G. Eine starke Stenose des Conus arteriosi dextri als Folge einem fibrosen parietalen Endocarditis. *Virchow's Arch. f. path. Anat.*, 267: 290, 1928.
38. Graham, C. S. and Griffiths, E. G. Stenosis of the pulmonary valve. *M. J. Australia*, 1: 51, 1929.
39. Garrison, R. E. and Feldt, R. H. Congenital pulmonary stenosis with closed cardiac septa: report of a case with comments regarding circulation time. *Am. Heart J.*, 24: 685, 1942.
40. Masselot, F., Baugas, J. and Girandon, C. Rétrécissement infundibulaire et orificiel de l'artere pulmonaire datant de l'enfance avec cyanose apparue à 40 ans. *Rev. Tunis. de Sc. Méd.*, 21: 117, 1927.
41. Andrewes, F. W. Two specimens of rare forms of congenital malformation of the heart. *Tr. Path. Soc. London*, 54: 144, 1903.
42. Bissell, W. W. Remarks accompanying a demonstration of two hearts with patent interventricular septum, extensive shortening of the colon and ulceration and huge calculus, dilatation of the ductus pancreaticus Wirsungi. *Tr. Chicago Path. Soc.* 9: 159, 1915.
43. Cochez, A. Rétrécissement de l'infundibulum de l'artere pulmonaire et communication interventriculaire sans troubles fonctionnels appreciables jusque l'age de vingt-six ans; cyanose, tuberculose pulmonaire. *Bull. Soc. med. de Hôp. Paris*, 13: 420, 1896.
44. Herzog. *München. med. Wchschr.*, 66: 1097, 1919.
45. Kurtz, C. M., Sprague, H. B. and White, P. D. Congenital heart disease; interventricular septal defect with associated anomalies in a series of three cases examined post mortem and a living patient fifty-eight years old with cyanosis and clubbing of fingers. *Am. Heart J.*, 3: 77, 1927.
46. Peacock, T. B. Contraction of the pulmonary orifice with imperfection of the septum ventriculorum, and an osseus state of the ductus arteriosus. *Tr. Path. Soc. London*, 7: 80, 1856.
47. Peacock, T. B. Great contraction, or stenosis of the pulmonary artery; defect in the septum of the ventricles and aorta arising equally from the two cavities; no ductus arteriosus; but that vessel replaced by two small cavities connected with the aorta. *Tr. Path. Soc. London*, 22: 88, 1871.
48. Rolleston, H. Congenital heart disease; pulmonary stenosis; patent septum ventriculorum. *Tr. Path. Soc. London* 43: 32, 1892.
49. Weiss, E. Congenital pulmonary stenosis with ventricular defect. *Tr. Path. Soc. Philadelphia*, 44: 73, 1924.
50. White, P. D. and Boyes, J. H. Subacute bacterial endocarditis and endocarditis involving the tricuspid valve and the pulmonary artery in a unique case of the tetralogy of Fallot complicated by congenital pulmonary regurgitation. *Am. Heart J.*, 7: 802, 1932.
51. White, P. D. and Sprague, H. B. Tetralogy of Fallot; case of a noted musician who lived to his sixtieth year. *J. A. M. A.*, 22, 787, 1929.
52. Harrison, W. F. Congenital heart disease; extreme congenital pulmonary stenosis; collateral pulmonary circulation; massive right-sided vegetative endocarditis. *Am. Heart J.*, 5: 213, 1929.
53. Leclerc and Michel. Rétrécissement pulmonaire; communication interventriculaire; bacillose pulmonaire. *Lyon méd.*, 122: 300, 1914.
54. Moore, N. Examples of malformation of the heart. *St. Bart. Hosp. Rep.*, 12: 101, 1876.
55. Raab, W., Weiss, R., Lowbeer, B. and Rihl, J. Untersuchungen über einem Fall von congenitalem Herzvitium. *Wien. Arch. f. inn. Med.*, 7: 367, 1924.
56. Stone, W. H. A case of tricoelian heart with insufficiency of the ventricular septu. *St. Thomas Hosp. Rep.*, 11: 57, 1882.
57. Talbott, J. H., Coombs, F. S., Castelman, B., Chamberlain, F. L., Consolazio, W. V. and White, P. D. A record case of the tetralogy of

Fallot with comments on metabolism and pathological studies. *Am. Heart J.*, 22: 754, 1941.

58. Segall, H. N. A case of tetralogy of Fallot: clinicopathological observations, quantitative studies of circulation rate and right to left shunt. *Am. Heart J.*, 8: 628, 1932.
59. Volini, I. F. and Flaxman, N. Tetralogy of Fallot; report of a case in a man who lived to his forty-first year. *J. A. M. A.*, 111: 2000, 1938.
60. Clarke, N. E. Bacterial endocarditis in congenital heart disease. *J. A. M. A.*, 81: 371, 1923.
61. Perlman, L. and Meyer, J. A case of tetralogy of Fallot with verrucous endocarditis. *Ann. Int. Med.*, 22: 121, 1945.
62. Schwedel, J. B. Clinical Roentgenology of the Heart. New York, 1946. Paul B. Hoeber. Pp. 324–328.
63. Millman S. and Kornblum, D. Interventricular septal defect wish dextraposition of the aorta without stenosis of the pulmonary artery. (Eisenmenger complex) complicated by subacute bacterial endocarditis. *J. Tech. Methods*, 15: 147 1936.
64. Stewart, H. L. and Crawford, B. L. Congenital heart disease with pulmonary arteritis. *Am. J. Path.* 9: 637, 1933.
65. Schramm, H. G. Schwere Herzmisbildungen bei älteren Individuen. *Beitr. z. path. Anat. u. z. allg. Path.*, 82: 153, 1929.
66. Abbott, M. E. On the incidence of bacterial inflammatory processes in cardio-vascular defects and in malformed semilunar cusps. *Ann. Clin. Med.*, 4: 189, 1923.
67. Baumgartner, E. A. and Abbott, M. E. Interventricular septal defect with dextraposition of aorta and dilatation of the pulmonary artery (Eisenmenger complex) terminating in cerebral abscess. *Am. J. M. Sc.*, 177: 639, 1929.
68. Talley, J. E. and Fowler, K. Tetralogy of Fallot (Eisenmenger type) with hypoplasia of the dextraposed aorta. *Am. J. M. Sc.*, 191: 618, 1936.
69. Saphir, O. and Lev, M. The tetralogy of Eisenmenger. *Am. Heart J.* 21: 31, 1941.
70. Dalrymple, J. Diseased heart in which the root of the aorta had an opening common to the 2 ventricles. *Tr. Path. Soc. London*, 1: 58, 1848.
71. Selzer, A. and Laqueur, G. Eisenmenger complex: report of two autopsied cases. To be published.
72. Selzer, A. and Carnes, W. H. The pathogenesis of persistent cyanosis. To be published.
73. Blalock, A. Physiopathology and surgical treatment of congenital cardiovascular defects. *Bull. New York Acad. Med.*, 22: 57, 1946.

Pure Congenital Pulmonary Stenosis and Idiopathic Congenital Dilatation of the Pulmonary Artery*

DAVID G. GREENE, M.D., ELEANOR DEFOREST BALDWIN, M.D., JANET STERLING BALDWIN, M.D., AARON HIMMELSTEIN, M.D., CHARLES E. ROH, M.D. *and* ANDRÉ COURNAND, M.D.

New York, New York

ENLARGEMENT of the pulmonary artery may be associated with any one of a variety of lesions, among which are interauricular septal defects, patency of the ductus arteriosus, mitral stenosis, chronic pulmonary disease, primary pulmonary arteriolar sclerosis and syphilis. Pure congenital pulmonary stenosis with poststenotic dilatation of the artery and idiopathic congenital dilatation of the pulmonary artery without stenosis are two of the less common causes of such enlargement.

During the past two years seven cases of pulmonary artery enlargement have been studied in the cardio-pulmonary laboratories of the Presbyterian Hospital and Bellevue Hospital. The clinical and physiologic diagnosis of pure pulmonary stenosis was made in three cases and of idiopathic dilatation of the pulmonary artery in four cases. One other case of pure pulmonary stenosis without a poststenotic dilatation of the pulmonary artery was also observed. As no attempt was made in either laboratory to make a special study of enlargement of the pulmonary artery the finding of these cases suggests that such congenital malformations are more common than hitherto suspected.

The purpose of this paper is to review the literature on pure congenital pulmonary stenosis and on idiopathic congenital dilatation of the pulmonary artery and to report the clinical and hemodynamic findings in four cases of each of these two conditions.

PURE CONGENITAL PULMONARY STENOSIS

Pulmonary stenosis is a common congenital heart lesion and one which is compatible with survival to adult life. It is frequently associated with defects of the interventricular septum and dextroposition of the aorta at its origin, the familiar tetralogy of Fallot. Pulmonary stenosis associated with an interauricular septal defect has been reported in a somewhat smaller group of cases.[2] Pure pulmonary stenosis, i.e., stenosis unassociated with abnormal communications between the greater and lesser circulation, is much rarer. In Maude Abbott's statistical analysis of 1,000 cases of congenital heart disease[2] pulmonary stenosis associated with a septal defect was found 101 times while pure pulmonary stenosis was found only nine times. In Gibson and Clifton's series of 1,950 autopsies on children under thirteen there were two cases of pure pulmonary stenosis[58] in a total of just over one hundred cases of congenital heart disease. Only sixty-eight examples of this condition proved by autopsy have been found in the literature.

Table I summarizes the most important findings of these cases. In this series only those cases

* From the Departments of Medicine and Surgery of the College of Physicians and Surgeons, Columbia University; the Department of Pediatrics, New York University and the Cardio-Pulmonary Laboratories of the Presbyterian Hospital and of the Chest Service of Bellevue Hospital, New York, N. Y. This work was supported in part through a grant of the Commonwealth Fund.

TABLE I

CHIEF CHARACTERISTICS OF SIXTY-EIGHT CASES OF PURE PULMONARY STENOSIS COLLECTED FROM THE LITERATURE

Author	Date	Age	Sex	Edema	Dyspnea	Cyanosis	Systolic Murmur	Systolic Thrill	Right Ventricular Hypertrophy	Infundibular Stenosis	Dilatation of Pulmonary Artery	Pulmonary Tuberculosis	Vegetative Endocarditis	Cause of Death
Philouze[100]	1826	....	M	+	..	..	..	..	+	..	+	0	0	heart failure
Chelius[30]	1827	26	M	+	+	+	+	..	+	..	0	..	..	heart failure
Burnet[24]	1830	7	F	+	..	+	+	+	+	..	0	..	..	heart failure
Elliotson[50]	1830	....	F	+	+	..	+	..	..	+	0	..	..	heart failure
Fallot[53]	1834	63	F	+	+	..	..	..	+	..	..	0	0	heart failure
Cruveilhier[38]	1835–1842	....	..	..	..	..	..	..	+	..	?	..	..	
Carswell[26]	1838	....	..	..	..	..	..	..	+	..	..	..	..	
Tiedemann[118]	1843	21	M	+	+	+	+	+	+	..	..	..	..	heart failure
Craigie[35]	1843	44	M	..	+	+	..	..	+	..	+	+	..	tuberculosis
Dittrich[41]	1849	20	M	..	..	..	+	+	+	+	0	..	?	
Ogle[91]	1853–1854	14	F	..	+	..	..	0	+	..	..	..	..	heart failure
Benedikt et al.[12]	1854	60	F	+	+	..	+	+	+	..	+	..	..	heart failure
Cejka[29]	1855	30	F	+	..	..	+	+	+	+	..	..	..	heart failure, stroke
Bernard[13]	1856	56	F	+	+	0	+	..	+	+	..			
Peacock[97]	1859	23	M	..	..	0	+	..	+	..	+	+		
d'Heilly[40]	1864	21	M	..	+	..	+	..	+	..	+	+	+	heart failure, endocarditis
Peacock[98]	1866	6	F	+	+	+	+	..	+	+	..	0	..	scarlet fever
Meynet[58]	1867	19	F	..	+	..	+	+	+	..	+	+	..	tuberculosis
Paul[95,96]	1871	36	M	0	..	0	+	..	+	..	+	+	..	tuberculosis
Solmon[110]	1872	31	M	..	..	..	+	..	+	..	+	+	..	tuberculosis
Budin[22]	1873	58	F	+	+	+	+	+	+	..	+	0	0	heart failure
Taruffi[116]	1875	21	M	..	+	+	+	+	+	..	+	+	..	tuberculosis
Letousey[85]	1877	24	M	..	+	0	+	..	+	..	0	+	0	tuberculosis
Duguet et al.[45]	1878	24	M	..	+	..	+	+	+	+	+	+	?	tuberculosis
Norman[89]	1878	26	M	..	..	+	..	..	+	..	..	..	..	sudden
Peacock[99]	1879	13	M	+	+	+	+	+	+	..	+	0	..	? heart failure, ? peritonitis
Havage[84]	1879	44	F	+	..	+	+	..	+	+	+	0	..	heart failure
Duguet[44]	1882	35	F	..	..	..	+	+	+	+	+	0	..	nephritis
Rinsema[102]	1884	34	M	+	..	0	+	+	+	..	0	0	0	heart failure
Flint[54]	1884	19	M	..	0	0	+	..	+	..	..	..	..	scarlet fever
Hebb[65]	1890	45	M	+	..	..	+	+	+	+	..	..	..	heart failure
La Fitte[79]	1892	21	F	+	+	0	+	+	+	+	0	+	+	vegetative endocarditis
Chrétien[32]	1893	19	M	..	..	0	+	..	+	+	0	0	..	sudden
Clarke[33]	1893	21	F	..	+	..	+	+	+	+	..	..	+	vegetative endocarditis
Ormerod[93]	1893	24	M	..	..	+	+	..	+	..	..	+	..	tuberculosis
Barié[13]	1895	43	F	..	..	..	+	+	+	+	+	+	..	Addison's disease
Rosenthal[104]	1896	16	M	+	+	+	+	+	+	..	+	0	..	erysipelas
Dresler[42,43]	1902–1904	2	F	0	0	0	+	+	+	..	0	0	0	cellulitis
Leclerc et al.[83]	1903	27	F	..	+	+	+	+	+	+	+	..	..	heart failure
Arnheim[5]	1905	5	M	+	+	0	+	+	+	..	+	+	0	heart failure
Josserand[72]	1906	22	F	+	+	+	+	0	+	..	+	..	..	heart failure
Genersich[57]	1907	18	M	..	+	..	+	+	+	+	+	+	..	tuberculosis
Dumas et al.[46]	1926	23	F	..	0	0	+	+	0	..	+	+	..	tuberculosis
Bishop et al.[14]	1929	32	F	+	+	0	+	mitral	+	..	0	..	+	vegetative endocarditis
Roesler et al.[103]	1931	46	F	+	..	..	..	..	+	..	..	..	?	
Arnett et al.[4]	1931	33	M	..	+	+	+	..	+	..	0	0	0	carcinoma
Abbott[1,2,48]	1932	12	M	+	+	+	+	+	+	+	+	0	0	heart failure
Abbott[1]	1932		F	+	..	0	..	..	+	+	0	0	+	vegetative endocarditis
Hertz[67]	1932	23	M	..	+	+	+	+	+	..	+	+	0	ruptured appendix
Ascarelli[6]	1932	70	M	..	..	..	..	..	+	..	+	..	..	cachexia
Leech[84]	1935	29½	..	+	..	..	+	..	+	..	..	..	..	heart failure
Bret[19]	1936	70	M	+	..	0	+	..	+	..	+	+	..	heart failure
Patino Mayer[94]	1936	14	M	0	..	+	+	+	+	..	..	..	+	vegetative endocarditis
Cabrera Calderín et al.[25]	1937	11	F	+	+	+	+	+	+	..	+	0	+	vegetative endocarditis
Ash et al.[7]	1939	14½	..	..	..	0	+	+	+	..	+	..	..	
Bonamour et al.[16]	1940	75	F	+	+	+	+	..	..	..	+	..	..	heart failure
Blackford et al.[15]	1941	23	M	..	+	+	+	+	+	..	+	0	0	
Garrison et al.[56]	1942	16	F	0	+	+	+	+	+	..	0	0	?	? vegetative endocarditis
Currens et al.[37]	1945													
Case II	1945	5½	F	..	0	0	+	..	+	..	+	0	0	subdural hematoma
Case IV	....	43	F	..	0	+	+	..	+	..	0	0	0	carcinoma, pellagra
Case VI	....	5½	F	..	0	+	+	+	+	..	0	0	+	osteomyelitis, septicemia
Case VII	....	5½	M	..	0	+	+	+	+	..	0	0	..	septicemia
Case VIII	....	16	M	..	+	+	+	+	+	..	0	0	0	heart failure
Case IX	....	24	F	..	+	0	+	+	+	..	0	+	0	heart failure
Case X	....	34	F	..	+	0	+	+	+	..	0	0	0	heart failure
Freed et al.[55]	1946	11½	F	+	0	+	+	+	..	..	+	..	..	heart failure
Lowance et al.[86]	1948	11	F	+	+	+	+	+	+	..	+	0	0	heart failure
Brock[20]	1948	20	F	+	..	..	..	..	..	..	..	..	..	operation

with anatomic confirmation have been collected. Both valvular and infundibular stenosis have been included. No cases with an abnormal communication between the pulmonary and systemic circulations have been used except when the foramen ovale has been described as a functionally closed slit. Most of the valvular lesions are clearly congenital in origin even though some of them were originally erroneously described as acquired.[81,99] Cases in which vegetative endocarditis is superimposed on an apparently previously normal valve or in which the original valve is destroyed have been excluded.[89] One case studied with the catheter technic has been omitted because pressures were not recorded in the pulmonary artery and anatomic confirmation was lacking.[69] Two cases demonstrated by angiocardiography were also omitted for lack of pathologic verification.[113]

In the absence of such elaborate studies insistence upon anatomic confirmation is essential, as Routier and Escalle[51,105–107] have recently demonstrated the inadequacy of the clinical diagnostic criteria of a typical pulmonic systolic murmur and thrill and roentgenologic evidence of pulmonary artery dilatation. Of the eighty-two cases they collected from the literature with this clinical picture only sixteen were found at autopsy to have pure congenital pulmonary stenosis.

Pathologic Findings. Pathologically, pure pulmonary stenosis can be divided into those cases in which the stenosis is at the infundibular area of the right ventricle and those in which the stenosis is at the valve itself.

In the first group the lesion results from an arrest of the normal process which ends in the incorporation of the bulbus cordis in the right ventricle as has been suggested by Keith.[73] The right ventricle is divided by a fibrous and muscular ridge into the main chamber and the infundibular portion leading to the pulmonary valve. This latter chamber may be dilated with thick muscular walls or may be a fairly narrow channel. The deformity is usually associated with an interventricular septal defect but seventeen cases were found in which no such defect was present. Five of these showed valvular stenosis as well.

In the second group with the stenosis only at the valve the deformity is strikingly similar in most of the cases. At the usual level of the pulmonary valve there is a diaphragm across the orifice, concave to the ventricle and projecting into the root of the pulmonary artery. In the center is a small hole a few mm. in diameter. The lesion has been compared to a cupola, the uterine cervix or to a *museau de tanche.* The outline of three semilunar valves can be seen in the diaphragm which appears as if it had been formed by the fusion of the edges of the three leaflets. The diaphragm may be fairly thin and pliable or may show some thickening and sclerotic changes. A smaller number of cases do not show the typical cupola but irregularly thickened and deformed leaflets, sometimes only two in number, with an irregular slit between them.

Stenosis of either the infundibulum or the pulmonary valve results in hypertrophy of the right ventricle which was a constant finding when mentioned, in all cases except that of Dumas and Pipard[46] in which it was specifically mentioned as being absent. At the time of death, particularly with heart failure, the right ventricle may be dilated with resultant tricuspid insufficiency and dilatation and hypertrophy of the right auricle. Sclerotic changes of the tricuspid valve are also frequently noted.

The main pulmonary artery beyond the stenotic valve may be normal in size but in about one-half of the cases it is dilated, sometimes to twice the normal diameter or more. The cause of poststenotic dilatation is not clear. Defective formation of the wall of the pulmonary artery and trophic changes have been suggested but not demonstrated. Cavina[25] produced partial pulmonary stenosis in young rabbits by tying a suture around the vessel. At autopsy, after a period of growth, the right ventricle and the pulmonary artery beyond the ligature were found to be much larger than those of controls of the same age. This suggests a mechanical explanation, perhaps associated with turbulent flow. A poststenotic dilatation is sometimes seen in an analogous relation to aortic stenosis.[62] In lesions such as the tetralogy of Fallot significant dilatation of the pulmonary artery is not common. Here the difference may be in the amount of blood going through the stenotic valve.

Clinical Findings. Frequently the only history given is that of the final illness, and the clinical histories are lacking in some of the cases. Of the sixty-four cases in which the sex of the patient is given thirty-three were females. The most common complaints were those of cardiac dysfunction, edema, dyspnea, palpitations and cyanosis. Some patients, however, suffered no

difficulties from their lesion for many years. In a few it was an incidental finding in the course of an examination for some other condition, particularly tuberculosis. Other patients first noted difficulties with the onset of an associated bacterial endocarditis. Cyanosis was present in twenty-eight of the cases, was specifically mentioned as not being present in eighteen and in twenty-two others was not mentioned at all. A few of the cyanotic patients were blue from early life while in many others cyanosis was noted terminally, perhaps with the onset of congestive failure. One remarkable woman reported by Bonnamour and Dumarest[16] first noted cyanosis at the age of forty. At sixty she began to have dependent edema and died of heart failure at the age of seventy-five. Arnett and Long[4] report one case of a thirty-three year old man in whom cyanosis first appeared two years before death. It was present in localized areas of the skin and not in the lips or fingernail beds. Arterial oxygen saturation was 94.6 per cent. They attributed the cyanosis in this man to stasis of blood in dilated minute blood vessels of the skin. He died of carcinoma without ever showing evidence of cardiac failure.

Clubbing of the digits was noted in only four cases and was specifically mentioned as absent in ten. Few blood counts are recorded but polycythemia was discovered in three patients and found to be absent in nine.

Examination of the heart shows a systolic murmur which is almost always loudest in the second or third left interspace close to the sternal border. In most cases there is no apparent correlation between the location of the murmur and the presence of infundibular versus valvular stenosis.[63] It is usually loud and may obscure the pulmonic second sound. Propagation toward the inner half of the left clavicle and to the interscapular region is usual and has been observed up the vessels of the neck. Propagation to the axilla was noted only once.[84] Occasionally the Valsalva maneuver results in decreased intensity of the murmur. The second pulmonic sound is usually not described but in nine patients it was softer than usual and in only two was it louder. A systolic thrill in the same area has been found in thirty-six cases. In a few cases a precordial bulge, especially in the pulmonic area, has been noted.

Electrocardiograms were taken in fourteen instances and in eleven of them right axis deviation was noted. In two there was no axis deviation and in one there was a right bundle branch block. P_1 and P_2, greater than 1 and 3 mm., respectively as described by Alexander et al.,[3] were sometimes observed. Of the twelve patients who were examined roentgenologically nine showed enlargement of the middle arc of the left border of the cardiac silhouette in the postero-anterior position, thought to be due to enlargement of the pulmonary artery. In two of these the enlargement was slight.

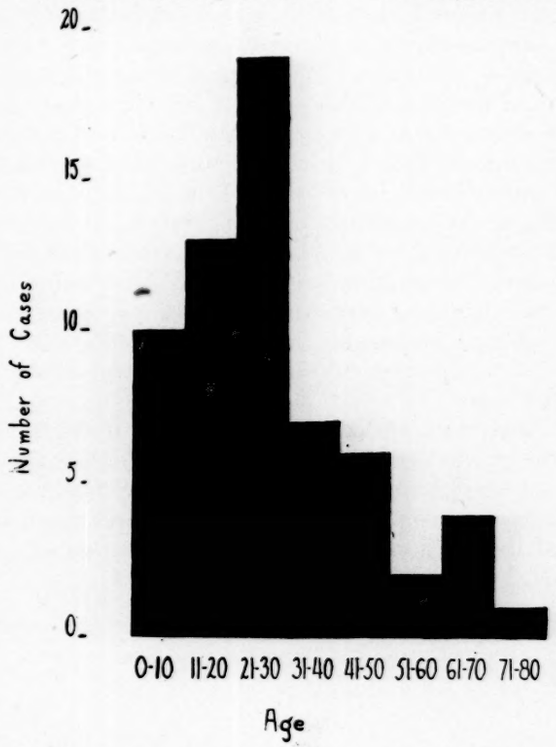


FIG. 1. Age in years at death by decades of sixty-two cases of pure congenital pulmonary stenosis collected from the literature. Brock's patient, who died at twenty, is not included.

Of the sixty-three cases in which the age at death is reported the average length of life was twenty-six years. Figure 1 shows the age at death of this group by decades. Only seven of the patients reached the age of fifty; of these three lived to be seventy. It is thus apparent that the lesion is compatible with survival to adult life but that 89 per cent of the patients die before they reach fifty. Heart failure was the greatest single cause of death, accounting for at least twenty-six of the deaths in this series. Tuberculosis of the lungs was the cause of death in ten and bacterial endocarditis in eight. In six cases the cause of death could not be determined from the data given.

In the older literature the association of pulmonary tuberculosis and pulmonary stenosis was frequently emphasized. Grenet and Francois-Joly[60] attacked these early figures on the ground that the tuberculosis was not confirmed either radiologically or bacteriologically. Aubertin[8] found a high incidence of family history of tuberculosis in a series of patients with both lesions. He quotes many opinions on the question, most of which support his view that the coincidence is fortuitous. Auerbach and Stemmerman[9] found thirteen cases of congenital heart disease in a tuberculosis institution. Of the seven autopsied cases all showed pulmonary stenosis but were also associated with other cardiac anomalies. A review of our series of cases from the literature shows that most of the eighteen cases were from earlier reports at a time when tuberculosis was more common than it is now.

Bacterial endocarditis definitely terminated the course of at least eight of the collected cases and was possibly present in four more. It did not differ from other cases of bacterial endocarditis of the right heart and embolic phenomena in the lungs were frequently present.

The creation of an anastomosis of the Blalock-Taussig type would not be expected to help these patients.[117] Their difficulty is not inadequate pulmonary blood flow but rather an abnormal burden on the right ventricle. Valvulotomy in the cases in which the valve alone is involved would seem in theory to be the ideal operation. In the one reported case in which this has been tried[20] the patient was in poor condition before surgery and died at operation before the valvulotomy could be performed. Three successful valvulotomies in patients with tetralogy of Fallot indicate, however, that the surgical approach to this area is perfectly feasible.[20]

PURE CONGENITAL DILATATION OF THE PULMONARY ARTERY

Pathologic Criteria. The pathologic diagnosis of pure congenital dilatation of the pulmonary artery is one which can be made only after various other associated lesions have been eliminated. Septal defects, mitral disease and patency of the ductus arteriosus are obvious lesions which are usually not overlooked. Other possible causes such as primary pulmonary arteriolar sclerosis and some forms of chronic pulmonary disease are more difficult to eliminate, particularly in incomplete reports. With the usual technic of removal of the heart at autopsy, cutting across the pulmonary artery close to its origin, borderline degrees of dilatation may easily be missed. Therefore, no attempt has been made to exhaust the earlier literature which has been covered in several reviews.[17,34,38,66] Eight cases with autopsy confirmation have been selected from the literature of the last thirty years as satisfying the following criteria: (1) simple dilatation of the pulmonary trunk, with or without involvement of the rest of the arterial tree; (2) absence of abnormal intra- or extracardiac shunts; (3) absence of chronic cardiac or pulmonary disease, either clinically or at autopsy; (4) absence of arterial disease, such as syphilis or more than minimal atheromatosis or arteriolar sclerosis.

Gold[59] has restricted the diagnosis of congenital dilatation of the pulmonary artery to cases in which there is concomitant hypoplasia of the aorta. If this is done, even fewer of these cases are acceptable. It would seem, however, that exclusion of a congenital dilatation of the pulmonary artery with an aorta of normal size puts too much emphasis on theoretical developmental grounds. We agree with Gold that the cases of Jennes,[71] Norris,[90] East[49] and of DeNavaquez *et al.*[39] are not clearly congenital in origin. Gold's own case was not included because of the extensive arteriolar changes described. A few cases have recently been diagnosed during life by the method of angiocardiography[61,113] but these have not been included.

Clinical Findings. Reference to Table II will show that in the selected cases there were six females and two males with a wide age distribution which included several patients of advanced years. Cyanosis was mentioned as being present three times and absent once. In the three cases in which the pulmonic second sound was described

it was normal once and accentuated twice. Aortic hypoplasia was present in three cases. In one patient the absence of right ventricular hypertrophy was specifically noted. There was one death from pulmonary tuberculosis while the two youngest patients died of congestive heart failure. It is thus apparent that pure congenital dilatation of the pulmonary artery is compatible with survival to middle or old age and that it may produce little functional difficulty.

TABLE II

CHIEF CHARACTERISTICS OF EIGHT CASES OF IDIOPATHIC DILATATION OF THE PULMONARY ARTERY COLLECTED FROM THE LITERATURE

Author	Date	No.	Age	Sex	Edema	Dyspnea	Cyanosis	Systolic Murmur	Systolic Thrill	Right Ventricular Hypertrophy	Pulmonary Tuberculosis	Hypoplasia of Aorta
Cautley[27]	1920	..	3/12	F	..	+	+	..	..	+	..	..
Sutherland[114,115]	1922	..	4	F	+	+	+	+	+	+	..	..
Esser[52]	1932	..	23	F	..	..	..	..	..	..	+	0
Oppenheimer[92]	1933	..	46	M	..	+	..	..	..	..	..	+
			60	F	..	+	+	..	..	+	..	+
Kourilsky[75]	1941	4	82	F	..	..	0	..	..	..	..	+
		9	54	M	..	..	..	+	..	0	..	0
Kourilsky[76]	1942	9	62	F	..	..	..	..	..	+	..	0

OBSERVATIONS IN EIGHT CASES

The eight subjects of the present report were children or young adults referred to the cardio-pulmonary laboratories at Bellevue Hospital or to the Presbyterian Hospital for study of congenital heart disease. Beside the usual history, physical examination and electrocardiographic, x-ray and fluoroscopic examinations each patient was studied by the technic of venous catheterization. Anatomic verification is available in Case v in which surgical exploration was carried out. As will be discussed later, however, physiologic studies clearly confirm the diagnosis in each case.

Clinical Findings. The histories of all eight patients were quite similar in that there were few or no subjective cardiac complaints. Two young girls complained of dyspnea on exertion but in each case this seemed to bear more relation to anxiety about their hearts than to any functional handicap and in each case it disappeared with reassurance. There was no history in any case of dependent edema or of cyanosis.

Examination showed a chest deformity in two patients. All eight patients had a systolic murmur in the pulmonic area and one had a pulmonic diastolic murmur as well. In four the second pulmonic sound was louder than normal and in one it was diminished. All but one patient showed a prominent pulmonary artery by x-ray. (Figs. 4 to 17.) There were two electrocardiograms which showed right axis deviation. The main findings are tabulated in Table III. The cases have been divided into two groups corresponding to the clinical diagnosis of pulmonary stenosis and pulmonary dilatation. This distinction is based essentially on the results of the physiologic studies.

Physiologic Data. Hemodynamic studies were conducted in each patient using the method of cardiac catheterization. Samples of blood were obtained from the catheter and from an indwelling needle in a systemic

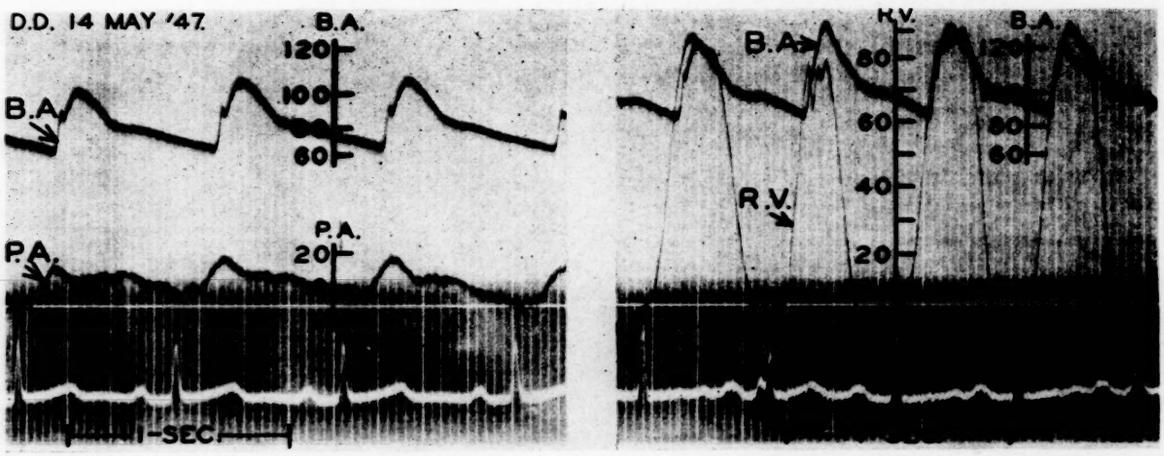


FIG. 2. Pressure tracingsin Case I. Note the low systolic pressure in the pulmonary artery (P.A.) and the high systolic pressure in the right ventricle (R.V.).

artery and were analyzed by the method of Van Slyke and Neill. Expired air was collected in a Tissot gasometer and samples analyzed by the method of Haldane. Pressures were recorded optically with Hamilton manometers. The two youngest patients were studied under rectal avertin anesthesia.

Three patients in this series performed a mild supine exercise after observations at rest had been made. Pressure readings were taken just before the exercise was started and intermittently during and after exercise. After two to five minutes, while exercise was continued, blood samples and gases were collected for the measurement of cardiac output. In Cases IV and VI the catheter tip was in the right auricle during the exercise and in Case VII it was in the pulmonary artery.

RESULTS

The results of the hemodynamic studies are shown in Tables IV and V. At rest the features common to all eight patients were:

TABLE III

CLINICAL OBSERVATIONS. GROUP I: FOUR CASES OF PURE PULMONARY STENOSIS
GROUP II: FOUR CASES OF IDIOPATHIC DILATATION OF THE PULMONARY ARTERY

Case	Age	Sex	Edema	Dyspnea	Cyanosis	Systolic Murmur	Systolic Thrill	Infundibular Stenosis	Dilatation of Pulmonary Artery	Pulmonary Tuberculosis	Vegetative Endocarditis	Accentuated Pulmonic Second Sound	Right Axis Deviation	Hypoplasia of Aorta
Group I														
I	8	F	0	0	0	+	+	+	+	0	0	−	+	0
II	22	M	0	0	0	+	+	+	+	+	0	n*	0	+
III	15	M	0	0	0	+	+	0	0	0	0	n	0	0
IV	19	M	0	0	0	+	+	..	+	0	0	n	0	0
Group II														
V	17	F	0	0	0	+	0	..	+	0	0	+	0	0
VI	14	F	0	0	0	+	0	..	+	0	0	+	0	+
VII	13	F	0	0	0	+	+	..	+	0	0	+	0	0
VIII	6	F	0	0	0	+	+	..	+	0	0	+	+	0

* n = normal.

(1) constancy within 6 cc. per L. in the individual case of the values for oxygen content of the mixed venous blood samples obtained through the catheter in rapid succession with maintenance of a steady state, (2) normal arterial oxygen saturation, (3) a significant difference between the right ventricular and pulmonary arterial systolic pressures. (Figs. 2 and 3.) In addition it should be noted that Case II shows evidence of congestive right heart failure as indicated by a high right ventricular diastolic pressure and right auricular mean pressure. In the other seven patients the right auricular mean pressure is normal.

From the oxygen contents of the mixed venous bloods the presence of a left to right shunt can be eliminated. There is no evidence of contamination with oxygenated blood in any case. In cases I and V no vena caval samples were obtained but the low saturation of the mixed venous blood (less than 75 per cent) rules out a left to right shunt. The normal arterial oxygen saturation in each case eliminates a right to left shunt of any size.

TABLE IV

PHYSIOLOGIC OBSERVATIONS. GROUP I: FOUR CASES OF PURE PULMONARY STENOSIS
GROUP II: FOUR CASES OF IDIOPATHIC DILATATION OF THE PULMONARY ARTERY

Case	Oxygen Content of Blood cc./L.						Arterial O_2 Saturation (%)	Cardiac Output (L./min.)	Cardiac Index (L./min./m^2BS)	Pressures (mm. Hg)			
	SVC	IVC	RA	RV	PA	AO				PA	RV	Mean RA	AO
Group I													
I	...	....	112	112	114	152	95	4.78	....	15/4 22/7 32/17	92/6	1	103/64
II	113	135	126	120	124	172	92	....	2.76	23/10	>60/12*	8	136/71
III	94	103	100	97	103	129	94	....	5.42	23/13 24/14	59/4 56/6	5	172/87
IV	139	155†	152	149	155	196	96	....	3.40 3.70	18/7 24/7	45/7 48/7	4	135/76 138/76
Group II													
V	...	....	117	116	116	158	98	....	3.10 4.10	15/0	33/1	−3	130/70‡
VI	121	136	136	134	133	167	99	....	3.90 4.20	17/4	31/6 28/3	1	126/71
VII	132	139	145	141	146	175	96	....	3.90 3.88	20/6 16/7	27/4 28/4	2	121/71 138/83
VIII	117	103	112	115	115	156	98	3.10	....	14/4 15/7	22/2	...	106/60

* Systolic pressure beyond the edge of the recording paper, exact height unknown.
† At entrance of inferior vena cava into right auricle.
‡ Measured by auscultation in arm.
SVC = superior vena cava; IVC = inferior vena cava; RA = right auricle; RV = right ventricle; PA = pulmonary artery; AO = systemic artery; m^2 BS = square meters body surface.

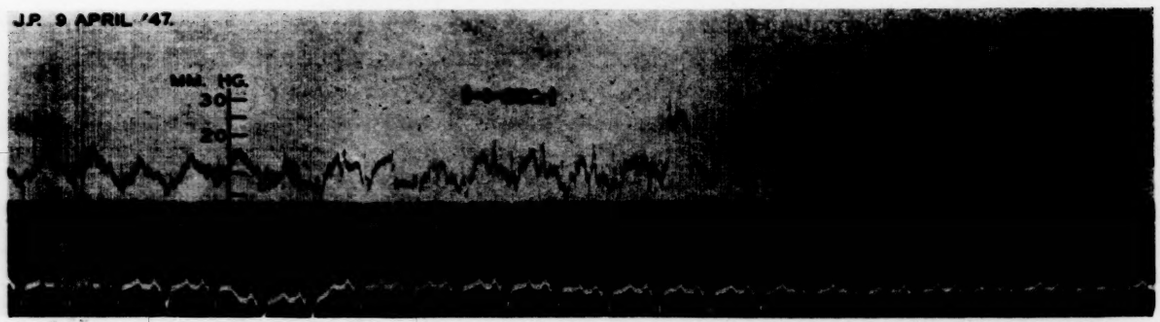


FIG. 3. Pressure tracing taken as the catheter tip was withdrawn from the pulmonary artery into the right ventricle, Case VIII. Note the low systolic pressure in the pulmonary artery and the higher but normal systolic pressure in the right ventricle.

During exercise there were no significant changes noted in the right auricular or pulmonary arterial pressures even though the blood flow increased significantly. All three patients showed an increase in the arteriovenous oxygen difference as well as an increased oxygen consumption. This is a normal response.

Description of the individual cases follows:

CASE REPORTS

CASE I. D. D., an eight year old school girl, was seen at Bellevue Hospital because of a heart murmur which was discovered at the age of six years during her first school examination. She had developed normally and had no complaints except for occasional easy fatigability.

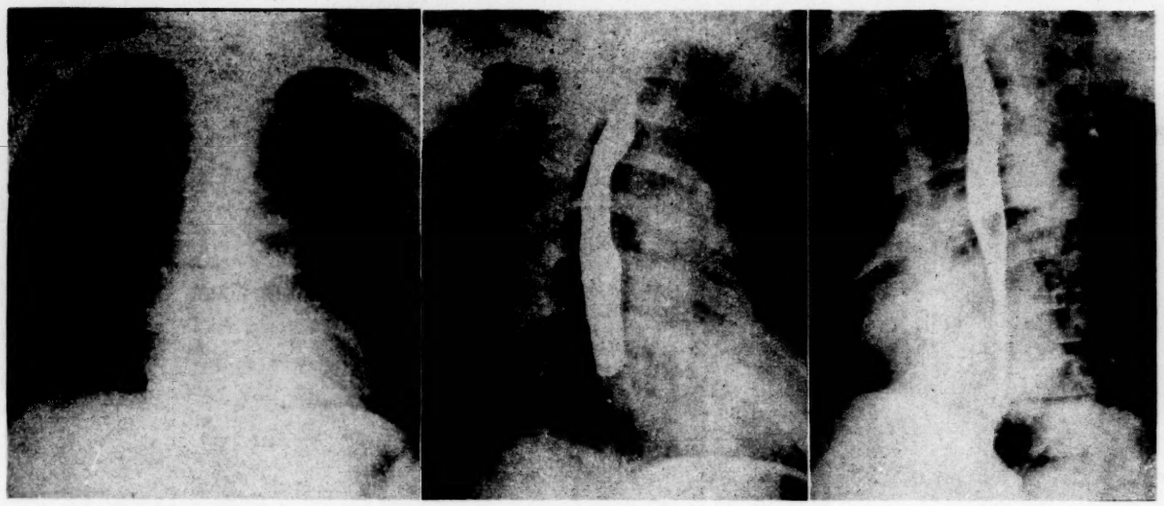
Physical examination showed normal development; there was no clubbing or cyanosis and no dyspnea even after moderately severe exercise. The heart showed slight enlargement to the left. There was a coarse systolic thrill close to the sternum in the third left interspace. The first sound was accentuated at the apex. The second sound was normal in intensity over the aortic area but very faint over the pulmonic area. There was a loud coarse systolic murmur over the upper left precordium which was loudest in the third left interspace at the sternal border and transmitted slightly upward to the left. The blood pressure was 112/72 mm. Hg before exercise, 118/76 mm. Hg after exercise.

Fluoroscopy and roentgenograms (Figs. 4, 5 and 6) showed slight transverse enlargement of the heart, with the apex lifted above the diaphragm. In the region of the pulmonary arc in

TABLE V

PHYSIOLOGIC OBSERVATIONS IN ONE CASE OF PURE PULMONARY STENOSIS AND TWO CASES OF IDIOPATHIC DILATATION OF THE PULMONARY ARTERY—RESPONSE TO SUPINE EXERCISE

Case	State	O_2 Consumption (cc./min.)	Arteriovenous O_2 Difference (cc./L.)	Stroke Volume (cc.)	Cardiac Index (L./min./m^2 BS)	Right Auricular Mean Pressure (mm. Hg)	Pulmonary Arterial Mean Pressure (mm. Hg)
IV	Rest	270	44	99	3.4	–	..
	Rest	285	42	94	3.7	3	..
	Exercise	1180	53	174	12.2	3	..
VI	Rest	209	39	61	3.9	–	..
	Rest	224	39	65	4.2	1	..
	Exercise	442	54	71	6.0	0	..
VII	Rest	232	37	58	3.9	..	13
	Rest	231	37	60	3.9	..	10
	Exercise	614	82	55	4.7	..	14



4 5 6

FIG. 4. Roentgenogram of the patient's chest in Case I, postero-anterior projection.
FIG. 5. Roentgenogram of the patient's chest in Case I, right anterior oblique projection. The esophagus is outlined with barium.
FIG. 6. Roentgenogram of the patient's chest in Case I, left anterior oblique projection. The esophagus is outlined with barium.

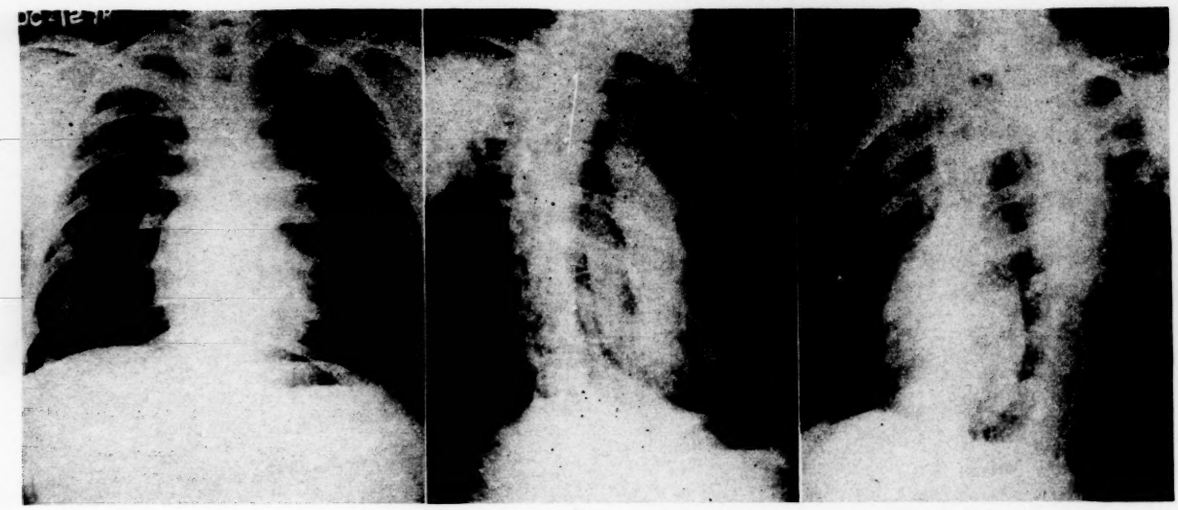
the postero-anterior view there was a prominent rounded shadow which, however, showed very little pulsation; a slight concavity was present immediately below this shadow. In the right anterior oblique view there was some flattening in the region of the outflow area of the right ventricle while above this there was prominence of the pulmonary artery. In the left anterior oblique view moderate enlargement of the right ventricle was apparent. There was no increase in the vascular markings in the lung fields. The electrocardiogram showed slight right axis deviation.

CASE II. F. P., a twenty-two year old white male, was admitted to the chest service of Bellevue Hospital for thoracoplasty for right upper lobe tuberculosis of four years' known duration. Heart disease had been discovered at ten years of age in elementary school, but the only symptom was easy fatigability on exertion. Cyanosis had never been noted.

Physical examination showed a sternal depression, with considerable forward bulging of the chest close to the sternum. Examination of the lungs showed signs of a right upper lobe cavity. The second pulmonic sound was louder than the second aortic sound but not markedly accentuated. There was a long, loud, harsh, systolic murmur over the third and fourth left intercostal spaces, poorly transmitted to the axilla. It was audible in the second left interspace but was not so loud. A systolic thrill was palpable over the lower left sternal border. Fluoroscopic and x-ray examinations (Figs. 7, 8 and 9) showed an enlarged pulsating pulmonary artery and left main branch. The right pulmonary artery appeared small in size as did the aorta. No other vessels or heart chambers were abnormal in size. The electrocardiogram showed no axis deviation.

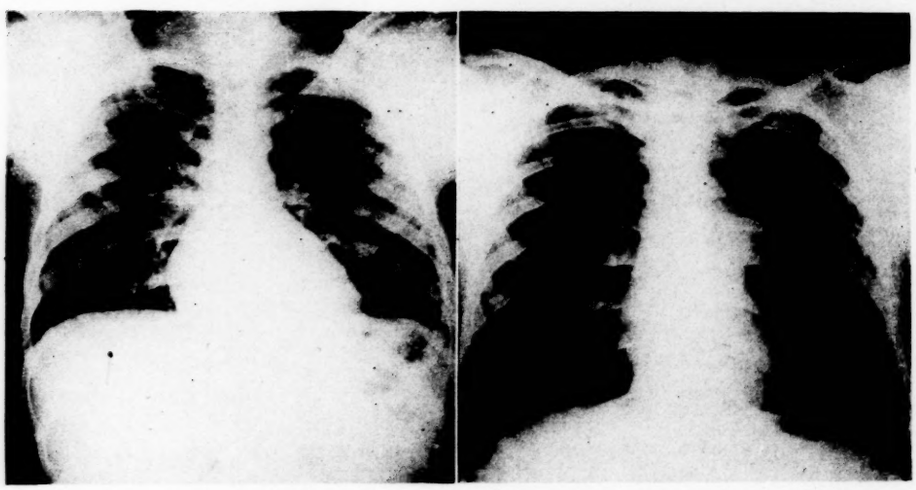
Six months previously angiocardiography had been performed at another hospital. This was reported to show enlargement of the main pulmonary artery and its left branch. The diameter of the ascending aorta was less than that of the pulmonary artery. The descending aorta was half the diameter of the ascending aorta and appeared hypoplastic. There was no evidence of abnormal shunts.

CASE III. S. S., a fifteen year old colored male who was admitted to Bellevue Hospital because of lobar pneumonia, had been told that he had had heart trouble since birth. He had no rheumatic history. His only cardiac complaint was mild dyspnea while playing basketball. Aside from the signs of pneumonia, the physical examination showed an audible but not accentuated pulmonic second sound. A systolic murmur was loudest over the midsternum but was transmitted along the clavicle and into the left interscapular region. It was accentuated during deep inspiration. Above



7 8 9

FIG. 7. Roentgenogram of the patient's chest in Case II, postero-anterior projection.
FIG. 8. Roentgenogram of the patient's chest in Case II, right anterior oblique projection.
FIG. 9. Roentgenogram of the patient's chest in Case II, left anterior oblique projection.



10 11

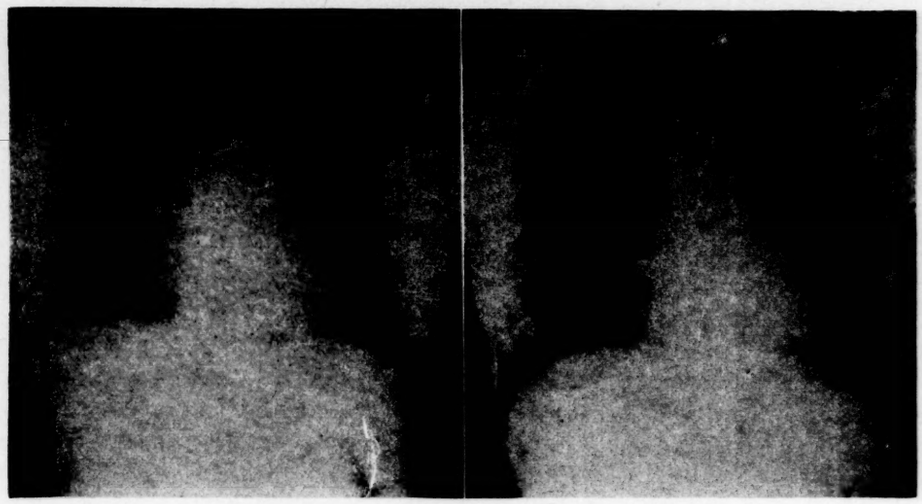
FIG. 10. Roentgenogram of the patient's chest in Case III; note the absence of enlargement of the pulmonary artery.
FIG. 11. Roentgenogram of the patient's chest in Case IV.

the right clavicle there was a systolic thrill. Fluoroscopy showed increased pulsations of the middle third of the left border of the heart and of the ascending aorta. There was questionable enlargement of the ventricles on x-ray examination. (Fig. 10.)

CASE IV. H. W., a marine aged nineteen, was referred to the Presbyterian Hospital for cardiac catheterization to rule out a patent ductus arteriosus. A heart murmur had been noted in infancy but he had been told he would "outgrow it." He had no complaints and his lesion had first been noted in a routine chest x-ray. (Fig. 11.)

Physical examination of the heart was negative except for a systolic murmur and thrill in the pulmonic area. The murmur was transmitted to the neck and to the interscapular region. The pulmonic second sound was not accentuated. The electrocardiogram was normal.

The patient had previously been studied at another hospital where angiocardiography was reported to demonstrate a markedly dilated left pulmonary artery. The main pulmonary



12 13

FIG. 12. Roentgenogram of the patient's chest in Case V.
FIG. 13. Roentgenogram of the patient's chest in Case VI.

artery and right branch were of normal size. The cardiac chambers and aorta were normal in appearance.

CASE V. E. L., a white salesgirl aged seventeen, was referred to the Presbyterian Hospital for surgical correction of a patent ductus arteriosus. Her activities had been limited because of "heart trouble," but she herself had only minor subjective complaints of dyspnea on exertion and occasional mild pains in the region of the left breast. She was able to go to school and to work as a salesgirl. Physical examination showed a normal heart except for a loud blowing systolic murmur best heard in the pulmonic area, not well transmitted elsewhere. The pulmonic second sound was louder than the aortic second sound. The laboratory findings, including an electrocardiogram, were normal. Roentgenologic examination showed an enlargement in the region of the pulmonary artery. (Fig. 12.)

In spite of the evidence against the presence of a patent ductus arteriosus obtained by catheterization, exploration was carried out. It was one of the earliest cases of suspected congenital heart disease studied by catheterization, and the value of the method had not yet been fully established.

At operation the pulmonary artery was found to be much dilated, and a thrill could be felt which seemed to originate in the region of the pulmonary valve. The ligamentum arteriosum showed no patent lumen. Convalescence was uneventful, and the patient was symptom-free and well when last seen nineteen months after the operation.

CASE VI. H. T., a white school girl aged fourteen, was referred to the Presbyterian Hospital because of an unusual cardiac silhouette discovered on routine x-ray examinations at school. A patent ductus arteriosus was suspected. She had no complaints. There was no history of cyanosis. Examination of the heart was normal except for a pulmonic systolic murmur which could be heard only after exercise. The pulmonic second sound was louder than the aortic second sound. The electrocardiogram was normal. X-ray showed an enlargement of the pulmonary artery. (Fig. 13.)

CASE VII. L. S., a thirteen year old white school girl, was referred to the Presbyterian Hospital with a possible case of patent ductus arteriosus. She had been well all her life, but on doctor's advice had refrained from games at the age of six. No reason was given for this restriction. Seven months before entry she noted slight exertional dyspnea, and after she was told by one doctor that she had rheumatic heart disease she complained of mild anterior chest pain. Immediately after this she began to have insomnia. These symptoms were completely relieved by reassurance. There was no history of cyanosis.

Physical examination showed an accentuated second sound in the pulmonic area and at the same point a systolic murmur and thrill. The

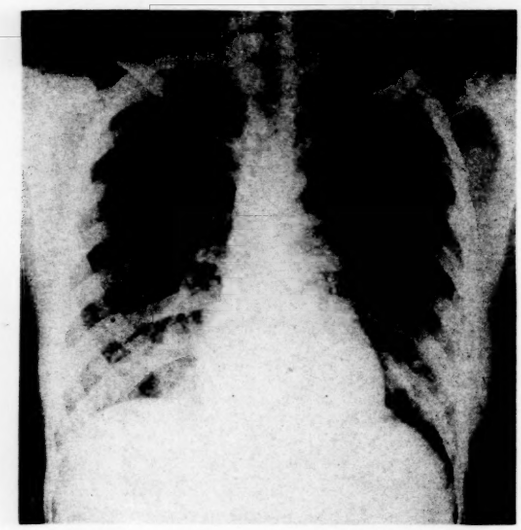


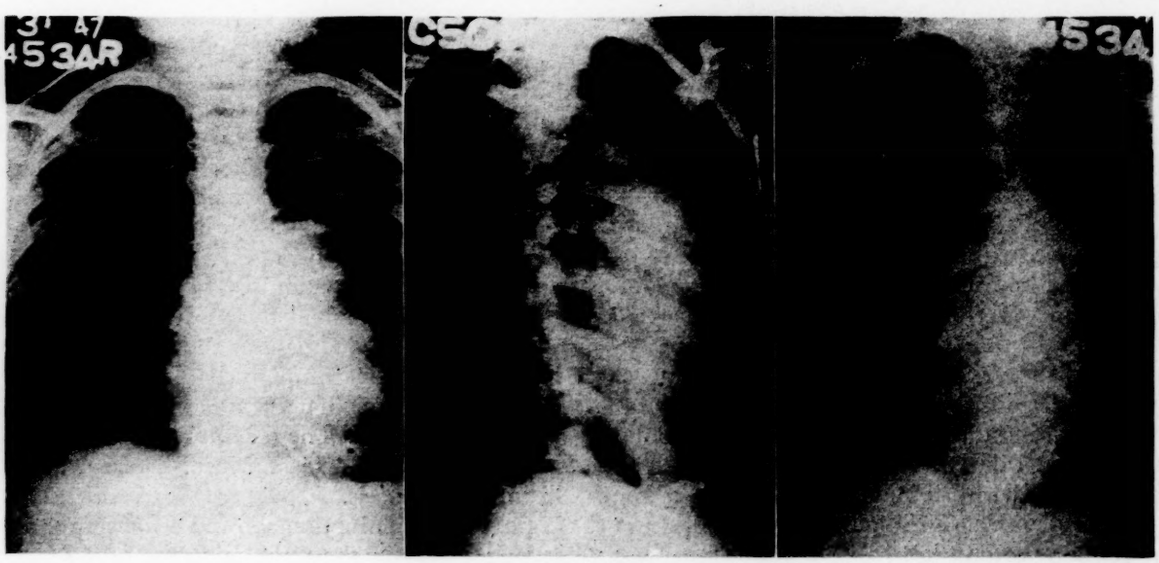
FIG. 14. Roentgenogram of the patient's chest in Case VII.

murmur was heard well all over the precordium and was transmitted to the vessels of the neck and faintly to the back. Fluoroscopy and x-ray examination showed an enlarged pulmonary artery with prominent pulsations. (Fig. 14.) The electrocardiogram was normal.

CASE VIII. J. P., a six year old girl, had been known since birth to have a heart murmur. She had developed normally but perhaps fatigued a little more easily than other children. Physical examination showed a funnel depression at the lower end of the sternum. No cyanosis or clubbing was present and no dyspnea after moderately severe exercise. The heart was slightly enlarged to the left at the apex, with an increase in width to the left at the base easily demonstrated by percussion. A systolic thrill was felt in the pulmonic area and the pulmonic second sound was very slightly accentuated. There was a loud, coarse systolic murmur heard best in the second left interspace, and an early less loud, blowing decrescendo diastolic murmur heard best in the third left interspace. The blood pressure was 105/70 mm. Hg before exercise, 112/75 mm. Hg after exercise. Fluoroscopy and x-ray examination of the heart showed a striking enlargement of the pulmonary artery and its left main branch; there was no enlargement of the other pulmonary vessels or "hilar dance." The apex of the heart was rounded and slightly lifted. (Figs. 15, 16 and 17.) The electrocardiogram showed slight right axis deviation and right bundle branch block.

COMMENTS

Normally the right ventricle and pulmonary artery are in free communication throughout most of systole and therefore the systolic pressure is the same. In the patients herein reported there is a significant drop between the systolic pressure in the right ventricle and that in the pulmonary artery. This drop of pressure may be



15 16 17

FIGS. 15, 16 and 17. Roentgenograms of the patient's chest in Case VIII; postero-anterior projection (Fig. 15); right anterior oblique projection (Fig. 16); left anterior oblique projection (Fig. 17).

related either to an organic pulmonary stenosis or to a simple dilatation of the pulmonary artery. In the first instance the presence of a narrow outlet causes hypertension in the right ventricle. In the second instance pressure is dissipated as the result of an abnormal deformability of the pulmonary artery and of its main branches due to dilatation and the thinness of the wall and because the flow at the site of the dilatation becomes turbulent. The systolic pressure in the right ventricle obviously should not be increased.

These cases may therefore be divided into two groups on the basis of the systolic pressure in the right ventricle:

Group I consists of pulmonary stenosis and group II consists of idiopathic dilatation of the pulmonary artery.

A mechanism suggested by Chisholm[31] may indicate that a stenosis of a particular type is present in simple dilatation of the pulmonary artery. He pointed out that the structures of the pulmonary orifice are easily stretched and when this orifice enlarges with dilatation of the pulmonary artery, the tissue most resistant to stretching is the free edge of the semilunar cusps. Then these free edges, instead of being closely applied to the arterial wall as they normally are during systole, may make three cords across the orifice and thus impede the flow of blood. This process, which he calls trigonoidation, Chisholm advances as the cause of a basal systolic murmur in patients with dilated pulmonary arteries. It seems possible that in addition to producing a murmur the taut edges of the leaflets might act to produce a slight degree of relative stenosis.

The grouping of these eight patients on the basis of pressure changes in the right ventricle corresponds to only one clinical sign. Three of the four patients in group I had normal pulmonic second sounds and in the fourth it was diminished in intensity. In group II the pulmonic second sound was accentuated in all four cases.

The results of the exercise are chiefly of interest in that they demonstrate the ability of the three patients tested to increase their cardiac output. This is particularly striking in Case IV in which the cardiac output was tripled. This illustrates very well the difference between pure pulmonary stenosis and the tetralogy of Fallot. In the latter at rest there is a right to left shunt and a consequent diminution of flow through the pulmonary artery. As this shunt increases with exercise the deficit of pulmonary blood supply increases. Holman and Beck[70] have demonstrated experimentally that pulmonary arterial stenosis is well tolerated, causing less cardiac muscle hypertrophy than a large interventricular shunt. In the clinical case with intact septa the entire output of the right heart goes to the lungs and as long as the right ventricle is able to overcome the obstruction to outflow no functional impairment results.

SUMMARY

1. Sixty-eight cases of pure congenital pulmonary stenosis without abnormal shunts, the diagnosis established at autopsy, have been collected from the literature and the chief clinical and anatomic features are described.

2. Eight cases of pure congenital dilatation of the pulmonary artery have been selected from the literature of the last thirty years as being unequivocal examples of that lesion and a summary of the clinical and anatomic features is given.

3. Four additional examples of each of these lesions are reported.

4. Hemodynamic studies of these eight patients demonstrate the absence of abnormal shunts and the presence of a differential between the systolic pressure in the pulmonary artery and that in the right ventricle.

5. A division of these patients into two groups on the basis of the pressure in the right ventricle and the intensity of the pulmonic second sound is proposed.*

* Since this paper was submitted for publication, three cases of pure pulmonary stenosis diagnosed by means of cardiac catheterization have been reported. POLLACK, A. A., TAYLOR, B. E., ODEL, H. M. and BURCHELL, H. B. Pulmonary stenosis without septal defect. *Proc. Staff Meet., Mayo Clin.*, 23: 516, 1948.

REFERENCES

1. Abbott, M. E. Congenital heart disease. In Nelson's Loose Leaf Medicine. Vol. 4, p. 207. New York, 1932. Thomas Nelson & Sons.
2. Abbott, M. E. Atlas of Congenital Cardiac Disease. New York 1936. The American Heart Association.
3. Alexander, A. A., Knight, H. F. and White, P. D. The auricular wave (P) of the electrocardiogram. Clinical observations with especial reference to pulmonic and mitral stenosis. *Arch. Int. Med.*, 36: 712, 1925.
4. Arnett, J. H. and Long, C. F. A case of congenital stenosis of the pulmonary valve with late onset of cyanosis. Death from carcinoma of the pancreas. *Am. J. M. Sc.*, 182: 212, 1931.
5. Arnheim, G. Ein Fall von angeborener Pulmonalstenose, sowie Bemerkungen über die Diagnose des offenen Ductus Botalli. *Berl. klin. Wchnschr.*, 42: 206, 1905.
6. Ascarelli, A. Intorno a un casa di ectasia aneurismatica dell'arteria polmonale. *Policlinico sez. prat.*, 39: 679, 1932.
7. Ash, R., Wolman, I. J. and Bromer, R. S. The diagnosis of congenital cardiac defects in infancy. *Am. J. Dis. Child.*, 58: 8, 1939.
8. Aubertin, Charles. Rétrécissement congenital de l'artère pulmonaire et tuberculose pulmonaire. *Paris méd.*, 1: 413, 1935.
9. Auerbach, O. and Stemmerman, M. G. Development of pulmonary tuberculosis in congenital heart disease. *Am. J. M. Sc.*, 207: 219, 1944.
10. Barié, E. Le rétrécissement pré-artériel de l'artère pulmonaire. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 12: 579, 1895.
11. Bauer, D. deF. and Astbury, E. C. Congenital cardiac disease. Bibliography of the 1000 cases analyzed in Maude Abbott's atlas. *Am. Heart J.*, 27: 688, 1944.
12. Benedikt, J. and Benedikt, E. Ein Fall von Insufficientia valv. semilun. arteriae pulmonalis. *Wien. med. Wchnschr.*, 4: 548, 1854.
13. Bernard, C. Quelques rémarques sur les lesions valvulaires des cavities droites du coeur, à propos d'un cas de rétrécissement siegeant dans le ventricule droit. *Arch. gén. de Méd.*, 8: 161, 1856.
14. Bishop, L. F., Bishop, L. F. Jr. and Wallace, S. C. Pulmonary stenosis with bacterial endocarditis in an adult. *Am. Heart J.*, 5: 238, 1929.
15. Blackford, L. M. and Parker, F. P. Pulmonary stenosis with bundle branch block; report of case with sound tracings and semiserial studies of conduction bundle. *Arch. Int. Med.*, 67: 1107, 1941.
16. Bonnamour and Dumarest. Sur un cas de rétrécissement pulmonaire congénital. *Lyon méd.*, 164: 182, 1940.
17. Boyd, L. J. and McGavack, T. H. Aneurysm of the pulmonary artery. A review of the literature and report of two new cases. *Am. Heart J.*, 18: 562, 1939.
18. Brenner, O. Pathology of the vessels of the pulmonary circulation. *Arch. Int. Med.*, 56: 211, 457, 724, 976, 1189, 1935.
19. Bret, Jean. Le rétrécissement pulmonaire à évolution prolongée. (Étude clinique d'après 27 observations nouvelle.) Lyon thesis, 1936.
20. Brock, R. C. Pulmonary valvulotomy for the relief of congenital pulmonary stenosis. Report of three cases. *Brit. M. J.*, 1121, 1948.
21. Brown, J. W. Congenital Heart Disease. London, 1939. John Bale & Staples, Ltd.
22. Budin, P. Rétrécissement acquis de l'orifice pulmonaire; pas de phthisie pulmonaire. *Bull. Soc. Anat. Paris.*, 8: 447, 1873.
23. Burke, Josef. Angeborene Pulmonalstenose. *Zeitschr. f. Heilkunde, Abtheilung f. Interne Medicin*, 23: 209, 1902.
24. Burnet. Observations de maladies du coeur. *J. Univ. Hebd. de Méd. et de Chir.*, 1: 65, 1830.
25. Cabrera Calderín, J. C. and Labourdette Scull, J. M. Un caso de endo-arteritis sub-aguda bacteriana en una estrechez pulmonar. *Bol. Soc. cubana de pediat.*, 9: 457, 1937.
26. Carswell, Robert. Pathological Anatomy. London, 1838. Longman, Orme, Brown, Green and Longman.
27. Cautley, Edmund. Congenital pulmonary regurgitation (transposition of the spleen). *Brit. J Child. Dis.*, 17: 187, 1920.
28. Cavina, Giovanni. Stenosi sperimentale dell'arteria polmonare. *Arch. per le sc. med.*, 39: 6, 1915.
29. Cejka. Drei Beobachtungen von Verwachsung des Herzbeutels. *Vierteljahrschrift f. d. prak. Heilkunde, Prague*, 46: 128, 1855.
30. Chelius, M. J. Drei Beobachtungen organischer Herzkrankheiten. *Heidelberger klin. Annalen*, 3: 412, 1827.
31. Chisholm, D. R. Trigonoidation of the semilunar valves and its relationship to certain basal systolic murmurs. *Am. Heart J.*, 13: 362, 1937.
32. Chrétien, E. Contribution à l'étude du rétrécissement pulmonaire préartérial acquis. *Rev. de méd.*, 13: 696, 1893.
33. Clarke, J. J. A case of ulcerative endocarditis associated with stenosis of the conus arteriosus affecting chiefly the pulmonary valve, with ulceration of the main pulmonary artery. *Tr. Path. Soc. London*, 44: 29, 1893.
34. Costa, A. Morfologie e patogenesi degli aneurismi dell'arteria polmonare. (Sopra un caso di voluminosi aneurismi multipli del tronco e dei grossi e medi rami, su base malformativa.) *Arch. di pat. e clin. med.*, 8: 257, 1929.
35. Craigie. Notice of a case of cyanosis, or the blue disease, connected with mutual adhesion of the semilunar valves of the pulmonary artery. *Edinburgh M. & S. J.*, 60: 265, 1843.
36. Cruveilhier, Jean. Anatomie Pathologique du Corps Humain. Paris, 1835–1842. J. B. Baillière.
37. Currens, J. H., Kinney, T. D. and White, P. D. Pulmonary stenosis with intact interventricular septum; report of eleven cases. *Am. Heart J.*, 30: 491, 1945.
38. D'Aunoy, Rigney and von Haam, Emmerich. Aneurysm of the pulmonary artery with patent ductus arteriosus (Botallo's duct). *J. Path. & Bact.*, 38: 39, 1934.
39. De Navasquez, S., Forbes, J. R. and Holling, H. E. Right ventricular hypertrophy of unknown origin: so-called pulmonary hypertension. *Brit. Heart J.*, 2: 177, 1940.

40. D'HEILLY. Des obliterations et rétrécissements congenitaux de l'artère pulmonaire. Paris thesis, 1864. Cited by Paul.[96]
41. DITTRICH. Die wahre Herzstenose, erläutert durch einen Krankheitsfall. *Vierteljahrschrift f. d. prak. heilkunde, Prague*, 21: 157, 1849.
42. DRESLER, K. Beitrag zur Diagnose der Persistenz des Ductus arteriosus Botalli. *Jahrb. f. Kinderh.*, 56: 705, 1902.
43. DRESLER, K. Nachtrag zur Diagnose der Persistenz des Ductus arteriosus Botalli. *Jahrb. f. Kinderh.*, 60: 571, 1904.
44. DUGUET. Rétrécissement de l'orifice artériel pulmonaire, non suivi de phthisie, chez une rhumatisante, hemiplégie faciale, néphrite parenchymateuse mortelle. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 19: 5, 1882.
45. DUGUET and LANDOUZY. Note sur un cas de rétrécissement acquis de l'artère pulmonaire chez un malade mort de tuberculose généralisée. *Bull. et mém. Soc. méd d. hôp. de Paris*, 15: 164, 1878.
46. DUMAS and PIPARD. Rétrécissement congénital de l'artère pulmonaire. *Lyon méd.*, 138: 49, 1926.
47. DUREY-COMTE, PIERRE. Contribution à l'étude du rétrécissement congénital de l'artère pulmonaire. Paris thesis, 1887.
48. EAKIN, W. W. and ABBOTT, M. E. Stenosis of the pulmonary conus at the lower bulbar orifice (conus a separate chamber) and closed interventricular septum with two illustrative cases. *Am. J. M. Sc.*, 186: 860, 1933.
49. EAST T. Pulmonary hypertension. *Brit. Heart J.*, 2: 189, 1940.
50. ELLIOTSON. The Recent Improvements in the Art of Distinguishing the Various Diseases of the Heart. London, 1830. Longman & Co.
51. ESCALLE, J. E. J. Etude critique du diagnostic clinique du rétrécissement congénital isolé de l'artère pulmonaire. Paris thesis, 1942.
52. ESSER, A. Seltene Formen von Aneurysmen. *Ztschr. f. Kreislaufforsch.*, 24: 737, 1932.
53. FALLOT. Quoted in *London M. & S. J.*, 5: 61, 1834.
54. FLINT, AUSTIN, SR. A specimen of stenosis of the pulmonary artery. *M. News*, 44: 287, 1884.
55. FREED, A. N. and BUDNITZ, J. Pure congenital plumonary stenosis. *Am. Heart J.*, 31: 369, 1946.
56. GARRISON, R. E. and FELDT, R. H. Congenital pulmonary stenosis with closed cardiac septa. *Am. Heart J.*, 24: 685, 1942.
57. GENERSICH, ANTAL. Stenosis ostii arteriosi dextri. Aneurysma trunci arteriae pulmonalis. *Orvosi hetil.*, 51: 614, 1907.
58. GIBSON, S. and CLIFTON, W. M. Congenital heart disease. *Am. J. Dis. Child.*, 55: 761, 1938.
59. GOLD, M. M. A. Congenital dilatation of pulmonary arterial tree; relation to Ayerza's disease and primary pulmonary arteriosclerosis. *Arch. Int. Med.*, 78: 197, 1946.
60. GRENET, H. and FRANCOIS-JOLY, J. Rétrécissement de l'artère pulmonaire et tuberculose. *Arch. de méd. d. enf.*, 39: 789, 1936.
61. GRISHMAN, A., STEINBERG, M. F. and OPPENHEIMER, B. S. The clinical diagnosis of idiopathic dilatation of the pulmonary artery. *J. Mt. Sinai Hosp.*, 10: 142, 1943–1944.
62. GRISHMAN, A., STEINBERG, M. F. and SUSSMAN, M. L. Congenital aortic and sub-aortic stenosis with associated anomalies of the aorta. *M. Clin. North America*, 31: 543, 1947.
63. GUINSBOURG, SARAH. Sur le frequence de la localization dans la troisième espace intercostal gauche du souffle systolique du rétrécissement pulmonaire. Paris thesis, 1914.
64. HAVAGE. Rétrécissement de l'artère pulmonaire et épanchement pericardique abondant. Absence de tubercules pulmonaires. Foie cardiaque. Néphrite mixte. *Bull. Soc. Anat. Paris*, 4: 562, 1879.
65. HEBB, R. G. Stenosis of pulmonary artery. Congenital heart disease. *Tr. Path. Soc. London*, 41: 57, 1890.
66. HENSCHEN, S. E. Das aneurysma arteriae pulmonalis. *Samml. Klin. Vort., Volkmann*, 422–33, *Innere Medizin N. F.*, 126–127, 1906.
67. HERTZ, THEODOR. Ein Fall von angeborener Pulmonalstenose ohne andere Dysplasien und Aplasien, mit positivem Deneke' schen Zeichen. *Ztschr. f. Kreislaufforsch.*, 24: 446, 1932.
68. HERXHEIMER, GOTTHOLD. In SCHWALBE, ERNST. Die Morphologie der Missbildungen des Menschen und der Tiere. Vol. 3, P. 401. Jena, 1910. Gustav Fischer.
69. HOWARTH, SHEILA, MCMICHAEL, J. and SHARPEY-SCHAFER, E. P. Cardiac catheterization in cases of patent interauricular septum, primary pulmonary hypertension, Fallot's tetralogy, and pulmonary stenosis. *Brit. Heart J.*, 9: 292, 1947.
70. HOLMAN, E. and BECK, C. S. Physiological response of circulatory system to experimental alterations; effect of aortic and pulmonic stenoses. *J. Clin. Investigation*, 3: 283, 1926.
71. JENNES, S. W. Diffuse aneurysmal dilatation of the pulmonary artery and both of its branches. *Bull. Johns Hopkins Hosp.*, 59: 133, 1936.
72. JOSSERAND. Rétrécissement de l'artère pulmonaire. *Lyon méd.*, 106: 674, 1906.
73. KEITH, ARTHUR. The Hunterian Lectures on malformations of the heart. *Lancet*, 2: 359, 433, 519, 1909.
74. KOEHLER, CURT. Beiträge zur Casuistik der Stenose des Ostium pulmonale. Halle thesis, 1894.
75. KOURILSKY, RAOUL, GUÉDÉ, MARCEL and REGAUD, JEAN. Les dilatations congénitales de l'artère pulmonaire. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 56: 772, 1941.
76. KOURILSKY, RAOUL, KOURILSKY, SIMONE, MARCHAL, MAURICE and GOUBERT, J. L. Sur le frequence relative des dilatations congénitales du tronc de l'artère pulmonaire. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 58: 246, 1942.
77. KOURILSKY, RAOUL, REGAUD, JEAN and DUGRENOT, HENRI. Erythrémie chez une malade atteinte d'une dilatation de l'artère pulmonaire. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 56: 762, 1941.
78. KOURILSKY, R., REGAUD, J. and RÉMOND, S. Verification anatomique d'un cas de dilatatiòn congénitale du tronc et des branches de l'artère pulmonaire, compliqué de stenose mitrale et d'atherome pulmonaire. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 58: 245, 1942.
79. LAFITTE, A. Rétrécissement infundibulaire de l'artère pulmonaire d'origine congénitale. Obliteration incomplète du trou de Botal. Absence

de cyanose. Endocardite végétante au niveau du rétrécissement. *Bull. et mém. Soc. Anat. de Paris*, 6: 13, 1892.

80. Laubry, Charles and Pezzi, C. Traité des maladies congénitales du coeur. Paris, 1921. J. B. Baillière.
81. Laubry, Charles, Routier, Daniel, Walser, J. and Doumer, Ed. Nouveau Traité de Pathologie Interne. III. Maladies du coeur et des vaisseaux. Paris, 1930. Gaston Doin & Cie.
82. Laubry, Charles. Discussion of Kourilsky.[77] *Bull. et mém. Soc. méd. d. hôp. de Paris*, 56: 770, 1941.
83. Leclerc and Barjon. Rétrécissement pulmonaire congénital. *Bull. Soc. méd. des Hôp. de Lyon*, 2: 463, 1903. Cited by Escalle[51] and Guinsbourg.[63]
84. Leech, C. B. Congenital heart disease. Clinical analysis of seventy-five cases from the Johns Hopkins Hospital. *J. Pediat.*, 7: 802, 1935.
85. Letousey. Rétrécissement de l'orifice de l'artère pulmonaire. *Bull. Soc. Anat. Paris*, 2: 472, 1877.
86. Lowance, M. I., Jones, E. C., Matthews, W. B. and Dunstan, E. M. Congenital pulmonary stenosis. *Am. Heart J.*, 35: 820, 1948.
87. Mayer, M. Über einen Fall von Stenosirung der pulmonal Arterie in Folge von acuter Endocarditis der semilunar Klappen. *Deutsches Arch. f. klin. Med.*, 24: 435, 1879.
88. Meynet, P. Rétrécissement de l'orifice de l'artère pulmonaire consecutif à une endocardite valvulaire: phthisie pulmonaire; mort. *Gaz. méd. de Lyon*, 19: 538, 1867.
89. Norman, H. B. Malformation of the pulmonary valves. *Brit. M. J.*, 2: 960, 1878.
90. Norris, R. F. Primary pulmonary arteriosclerosis. Report of a case with marked calcification of the pulmonary arteries. *Bull. Johns Hopkins Hosp.*, 59: 143, 1936.
91. Ogle, J. W. Abnormal condition of the valve at the root of the pulmonary artery, with consequent hypertrophy of the parietes of the right ventricle of the heart. *Tr. Path. Soc. London*, 5: 69, 1854.
92. Oppenheimer, B. S. Idiopathic dilatation of pulmonary artery. *Tr. A. Am. Physicians*, 48: 290, 1933.
93. Ormerod, J. A. Disease of pulmonary valve. *Tr. Path. Soc. London*, 44: 30, 1893.
94. Patiño Mayer, C. Endoarteritis y valvulitis ulcerovegetantes, en una estenosis congenita de la pulmonar. Infartos septicos multiples en ambos pulmones. *Semana méd.*, 2: 277, 1936.
95. Paul, Constantin. Du rétrécissement de l'artère pulmonaire contracté après la naissance. De ses symptoms et de ses complications. *Gaz. d. hôp. Paris*, 44: 202, 1871.
96. Paul, Constantin. Diagnostic et traitement des maladies du coeur. 2nd ed. Paris, 1887. Asselin and Houzeau.
97. Peacock, T. B. Contraction of the orifice of the pulmonary artery from fusion of the valves. *Tr. Path. Soc. London*, 10: 107, 1859.
98. Peacock, T. B. On Malformations of the Human Heart, etc. 2nd ed. London, 1866. J. C. A. Churchill, Ltd.
99. Peacock, T. B. Case of stenosis of the pulmonary artery from disease of the valves, probably of congenital origin. *Tr. Path. Soc. London*, 30: 258, 1879.
100. Philouze. Dilatation considérable de l'oreillette droite du coeur; ossification de l'orifice auriculo-ventriculaire droit; ossification et rétrécissement considérable de l'orifice de l'artère pulmonaire, dilatation enorme de cette artère; hypertrophie du ventricule droit, etc. *Bull. Soc. Anat. Paris*, 1: 158, 1826.
101. Potain and Rendu. Coeur (pathologie). Dechambre's Dictionnaire Encyclopedique des Sciences Médicales. 18: 619, 1876.
102. Rinsema, Th. Ein Fall von acquirirter Stenose des Ostium pulmonale. *Deutsches Arch. f. klin. Med.*, 34: 216, 1884.
103. Roesler, H. and Kiss, A. Beiträge zur Lehre von den angeborenen Herzfehlern. VII. Elektrokardiographische Untersuchungen an 100 Fallen. *Wien. Arch. f. Inn. Med.*, 21: 271, 1931.
104. Rosenthal, Johannes. Beitrag zur Casuistik der erworbenen Stenose der Pulmonalarterie durch Verwachsung der Klappensegel. Freiburg thesis, 1896.
105. Routier, D. Book revue. Escalle, J. E. Étude critique du diagnostic clinique de rétrécissement congénital isolé de l'artère pulmonaire. Paris thesis, 1942. *Arch. d. mal. du coeur*, 36: 24, 1943.
106. Routier, D. and Escalle, J. E. A propos du diagnostic clinique du rétrécissement pulmonaire. *Arch. d. mal. du coeur*, 36: 59, 1943.
107. Routier, D. and Escalle, J. E. A propos des signes d'auscultation du rétrécissement pulmonaire. *Arch. d. mal. du coeur*, 38: 284, 1945.
108. Schnitker, M. A. The Electrocardiogram in Congenital Cardiac Disease. Cambridge, 1940. Harvard University Press.
109. Scott, R. B. Aneurysm of the pulmonary artery with report of a case. *Lancet*, 1: 567, 1934.
110. Solomon, Raymond. Du rétrécissement pulmonaire acquis. Paris thesis, 1872.
111. Stölker, Carl. Beiträge zur Pathologie der angeborenen Stenose der Arteria pulmonalis. *Schweiz. Ztschr. f. Heilkunde*, 3: 3, 4, 1864.
112. Stölker, Carl. Ueber angeborene Stenose der Arteria pulmonalis. Bern, 1864. Haller.
113. Sussman, M. L., Grishman, A. and Steinberg, M. F. Newer concepts in the diagnosis of congenital heart disease. *Am. J. Dis. Child.*, 65: 922, 1942.
114. Sutherland, G. A. Symptoms and signs in chronic heart disease. *Brit. J. Child. Dis.*, 19: 1, 1922.
115. Sutherland, G. A. A case of congenital aneurysm of the pulmonary artery. *Brit. J. Child. Dis.*, 20: 27, 1923.
116. Taruffi, Cesare. Caso di stenosi acquisita dell'arteria pulmonare. *Bull. d. sc. med.*, 19: 225, 1875.
117. Taussig, H. B. Congenital Malformations of the Heart. New York, 1947. The Commonwealth Fund.
118. Tiedemann, Friedrich. Von der Verengung und Schliessung der Pulsadern in Krankheiten. Heidelberg and Leipzig, 1843. Karl Groos.
119. Whitley, G. Cases of disease of the pulmonary artery and its valves. *Guy's Hosp. Rep.*, 3: 252, 1857.

Aureomycin in the Treatment of Primary Atypical Pneumonia*

YALE KNEELAND, JR., M.D., HARRY M. ROSE, M.D. *and* COUNT DILLON GIBSON, M.D.
New York, New York

AUREOMYCIN is a new antibiotic derived from a Streptomyces by Duggar of Lederle Laboratories.[1] Preliminary studies[2] indicated that it was effective not only against a wide bacterial spectrum, both gram-positive and gram-negative, but also against rickettsial infections in experimental animals.[3] In addition it was shown to exert a curative action on two experimental virus infections in mice, lymphogranuloma venereum and psittacosis. Moreover, acute and chronic toxicity studies in animals indicated that it would in all probability be suitable for administration to human beings.

Since these early studies a few reports have appeared of its clinical use in the treatment of infections in man. It appears to be highly effective in all types of rickettsial disease thus far studied[4] and also in lymphogranuloma venereum.[5] A few citations of its use in bacterial infections have also appeared.[4] To date no important toxic side effects have been described.

We propose to report our experiences with this agent in the treatment of primary atypical ("virus") pneumonia. Atypical pneumonia cannot be differentiated on purely clinical grounds from Q-fever or from human infection with the psittacosis-ornithosis group of viruses. Q-fever was known to be susceptible to aureomycin and there was reason to suppose from experimental studies[3] that psittacosis also would be susceptible. Because of its known antiviral activity in these infections, aureomycin seemed worth a trial in primary atypical pneumonia. Therefore, in July, 1948, when one of us was called to see an extremely ill patient who presented the clinical features of atypical pneumonia, treatment with aureomycin was instituted. A small supply of aureomycin had been made available to us by Dr. Herald Cox of the Lederle Laboratories.

Results in this patient, to be presented below, seemed sufficiently encouraging to warrant further trial. It is obvious that in treating a disease like atypical pneumonia, which is so variable and unpredictable in its course, conclusions must be drawn with the utmost caution. Nevertheless, as case has succeeded case the impression has deepened that following the administration of aureomycin a modification in the clinical severity of the disease takes place with regularity. For this reason it seems justified to publish the data on our first ten cases of atypical pneumonia treated with aureomycin in the hope that they will stimulate other studies along this line.

SELECTION OF CASES

The criteria we have established as to the selection of cases for treatment are as follows: (1) The patient must present the familiar clinical features of cough, fever, pneumonitis, normal leukocyte count, normal bacterial flora of sputum, etc., (2) the disease must have been unaffected by penicillin in full doses for at least forty-eight hours and (3) the patient must be getting worse at the time treatment is instituted.

* From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York, N. Y.

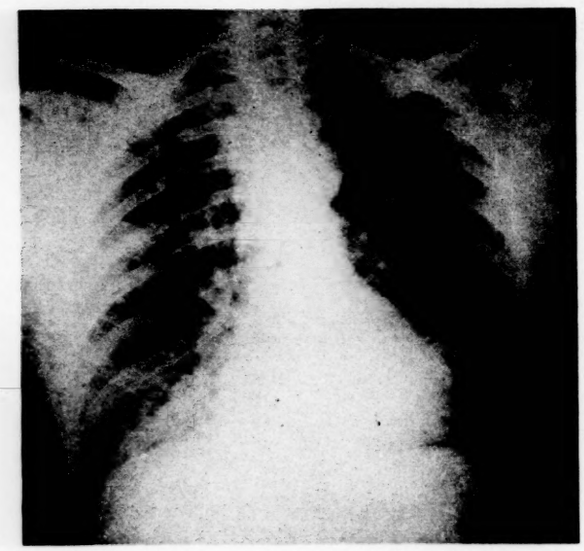


FIG. 1. Case I, chest x-ray taken on July 22nd, the day aureomycin treatment was started. Fairly extensive patchy infiltration of the right lung is evident.

DOSAGE OF DRUG AND METHOD OF ADMINISTRATION

Aureomycin hydrochloride may be injected parenterally by various routes but a wholly satisfactory vehicle has not yet been developed. The crystalline powder may be taken orally in capsules. When given in sufficient dosage by mouth, satisfactory blood levels are obtained and these are ordinarily maintained for at least six hours. The dosage we have employed has been somewhat varied. We have usually started treatment at a level of 4 Gm. daily in six-hourly divided doses, and then reduced this gradually in the succeeding days. Of late we have given an initial dose of 1.5 Gm., followed by 1.0 Gm. every six hours. In general, we have maintained the drug until the temperature has been down several days and the patient is substantially improved.

SIDE EFFECTS

Two of the ten patients developed nausea which seemed clearly related to the aureomycin. Vomiting often occurred an hour to an hour and a half after a dose in these two patients. It was not believed that this interfered materially with absorption. One patient presented anemia during convalescence. None of the other patients showed any serious untoward effects.

CASE REPORTS

CASE I. (Patient of Dr. C. D. Dunham). A forty-seven-year-old white woman entered the hospital on July 17, 1948, with a five-day history of chilliness, malaise, cough, fever, pain in the chest, headache and hoarseness. She gave no history of exposure to infectious disease, animals or possible insect vectors.

On admission she appeared acutely ill, but apart from a reddened pharynx the general physical examination was not remarkable. As shown in the accompanying graph the temperature was only 99.8°F. but rose promptly to 102°F. Pulse rate at this time was 96 and in general tended to be somewhat low in proportion to the fever; respirations were 22. Chest x-ray was negative; the white blood count was 8,650 with 64 per cent polymorphonuclears; urine was negative. Sputum was negative for acid-fast organisms and no significant pathogens could be cultivated.

For the next twenty-four hours the fever remained fairly constant at this level but in the early hours of July 19th, following a chill, the temperature rose to 104°F. At this time she appeared worse; there was severe paroxysmal cough, mostly unproductive, together with more malaise, weakness and headache. The leukocyte count at this time was essentially unchanged, blood culture was negative, and a repeat x-ray was interpreted as showing possibly a minimal pneumonitis at the right base. Her temperature fell on salicylates during the day but rose again and reached 105°F. on July 21st. During the first four days in the hospital she was treated with intramuscular penicillin, 600,000 units a day.

On July 22nd her condition appeared more serious. During the night she had been disoriented. She was prostrated and the cough was intermittently very severe. She appeared dyspneic and crepitant rales were noted over the right lower lobe. As shown in Figure 1, an x-ray now revealed a fairly extensive patchy pneumonitis on the right. The decision to treat with aureomycin was made in the afternoon and the first dose of 1.0 Gm. given at 5:00 P.M.

As indicated in Figure 2 the temperature fell during the next day, rose during the night of the 23rd to 103°F. and then fell again on the morning of the 24th to essentially normal levels.

With the exception of a minor elevation to 100.6°F. that afternoon it remained normal thereafter.

It was noted that on the day following the start of treatment the patient appeared somewhat stronger and better generally. By July 24th this improvement was striking. The headache had disappeared, cough was less distressing and there was considerable increase in strength and sense of well being. Convalescence thereafter was uneventful. Treatment with 4 Gm. daily of aureomycin was maintained for a total of seven days. X-ray (Fig. 3) on July 27th showed almost complete clearing of the pneumonitis.

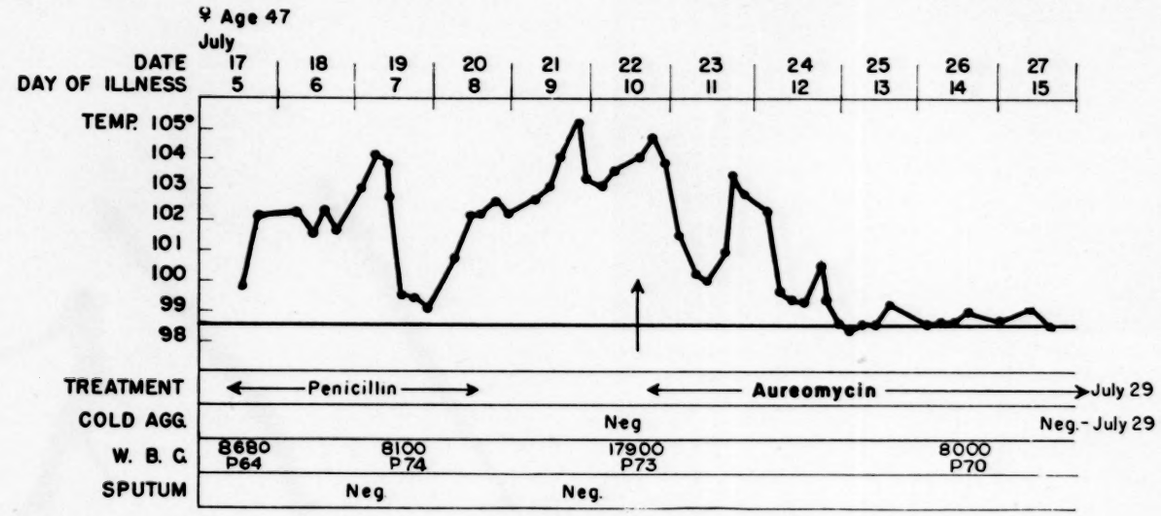


FIG. 2. Chart of Case I.

Serum specimens obtained at intervals during the acute illness and convalescence and tested for cold agglutinins were all negative. Complement-fixation tests for Q-fever and psittacosis were inconclusive. Thus we had no serologic clue to the etiology of this patient's disease. (Serologic tests for brucellosis, and the Weil-Felix and Widal tests were also negative.) Nevertheless we believed that the most probable diagnosis was primary atypical pneumonia of the familiar type.

The case was a rather severe one and all observers believed that aureomycin had an effect on its course, an effect, incidentally, similar in character to that described in Q-fever. The case has been reported in some detail because it was responsible for our subsequent trials of the antibiotic.

CASE II. The patient was a twenty-four year old student nurse who entered Harkness Pavilion on August 2, 1948. Three days earlier she had developed signs of an upper respiratory tract infection with nasal congestion and malaise. About thirty-six hours before admission a nonproductive cough commenced, together with headache and a feeling of feverishness. Not long thereafter she had a shaking chill with a rise in oral temperature to 102°F. At the time of admission to the hospital she was acutely ill with a severe paroxysmal cough and a temperature of 101.8°F.

The physical examination revealed numerous moist rales over the base of the right lung posteriorly, and the chest x-ray showed mottled shadows in the region of the right lower lobe. The leukocyte count was 8,400 with a normal differential. No sputum could be obtained for bacteriologic examination but the throat culture was negative for respiratory pathogens.

During the next three days the patient received penicillin, one million units every twenty-four hours. Despite this treatment the temperature mounted progressively to 103°F., the cough continued unabated, and the physical signs over the right lower lobe became more pronounced. Penicillin was therefore discontinued and aureomycin was started on the fourth hospital day in a dose of 1.0 Gm. every eight hours given by mouth. Over the next forty-eight hours the temperature fell to normal, the cough virtually ceased and the patient noted a marked increase in her sense of well being. By the end of the third day on aureomycin all symptoms had disappeared with the exception of a slight residual cough. At this time the supply of the drug became exhausted and treatment therefore had

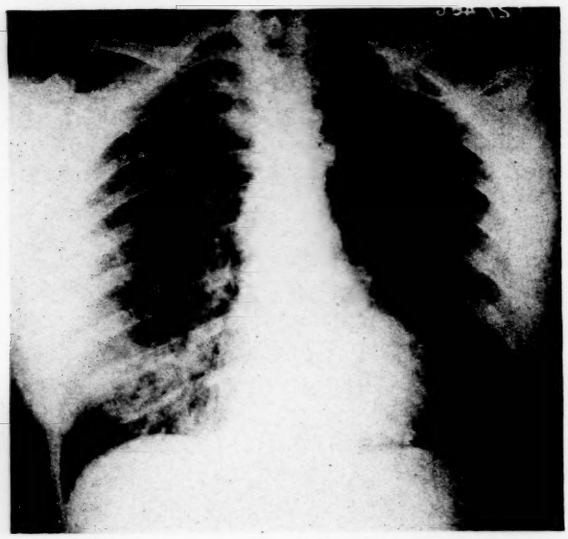


FIG. 3. Case I, x-ray taken on July 27th, five days later. A remarkable degree of clearing has taken place.

to be stopped. Twenty-four hours later the temperature rose again to 100.2°F. and continued to fluctuate between 99° and 100°F. for the following week. Cough recurred and there was evidence by x-ray of extension of pulmonary involvement. No further treatment was given and the illness finally subsided uneventfully after about ten days. The cold agglutinin test was negative on admission, August 2nd, but was positive in a serum dilution of 1:64 on August 21st.

The character of the illness, the failure to respond to penicillin and the development of cold agglutinins indicate that the patient probably suffered from primary atypical pneumonia. The administration of aureomycin was followed by a prompt defervescence of clinical signs and symptoms suggesting a specific therapeutic response to the drug. The fact that the disease relapsed soon after the premature cessation of treatment supports this possibility.

CASE III. The patient was a fourteen year old schoolboy who was attending a summer camp. On about July 15, 1948, he developed an acute pharyngitis with fever and a persistent hacking cough. The pharyngitis rapidly subsided but the fever and cough continued, and he was confined to the camp infirmary for two weeks with an intermittent temperature ranging between 100° and 102°F. By the end of that time, however, all symptoms had subsided and he was discharged from the infirmary on July 30th apparently recovered, but still running an afternoon temperature of 99° to 99.6°F.

One week later, on August 6th, he again became acutely ill and his temperature rose to 102°F. The following day he began to have a productive cough and complained of pain in the chest. On August 8th he was admitted to the hospital in Sharon, Connecticut, under the care of Dr. Graham B. Blaine, to whom we are indebted for permission to report the case. On entry to the hospital an x-ray of the chest showed patchy pneumonic involvement of the right upper and middle lobes. The leukocyte count was 9,000 with a normal differential. The blood was negative for cold agglutinins. Culture of the sputum revealed no respiratory pathogens. During the next four days, on treatment with penicillin and sulfadiazine, the cough decreased, the temperature fell to normal and on August 12th the x-ray showed marked clearing. On the following day, however, the temperature again spiked to 103°F., cough became more severe and chest pain returned. X-rays showed an extensive area of new pulmonary involvement in the region of the right lower lobe. Using doses of 0.3 Gm. every eight hours by mouth, treatment with aureomycin was begun on August 15th. Thirty-six hours later the temperature was normal, the cough and chest pain had ceased and the patient appeared much improved. Aureomycin was continued for an additional five days and recovery was uneventful. Another x-ray of the chest taken four days after the beginning of treatment with aureomycin showed almost complete resolution of the pneumonic process. A specimen of blood obtained during convalescence again was negative for cold agglutinins.

This patient had a relapsing febrile illness with a migratory type of pneumonitis, negative bacteriologic findings and absence of leukocytosis. Treatment with penicillin and sulfadiazine was apparently ineffective but the administration of aureomycin was followed by prompt defervescence of the disease. The diagnosis of primary atypical pneumonia seems fairly well established on clinical grounds, and it is known that cold agglutinins do not develop in about 25 per cent of cases. In addition, complement fixation tests for psittacosis and Q-fever were negative with both acute and convalescent phase blood specimens.

CASE IV. The patient was a thirty-eight year old colored female who entered the Presbyterian Hospital on August 30, 1948. Four days before admission she developed a hacking cough with

whitish, mucoid sputum. The cough became progressively worse and was accompanied by malaise, headache and a sensation of fever. On admission the temperature was 104.2°F. and the patient appeared acutely ill with a severe hacking cough productive of frothy, pinkish sputum.

The physical examination was essentially negative except for numerous moist rales over the right upper lobe. The white count was 10,900, with 84 per cent polymorphonuclears. The sputum culture was negative for significant pathogens. The blood culture was sterile. Penicillin was given for the first two days in a dose of 100,000 units every three hours without any apparent effect upon the course of the illness. For the first thirty-six hours the temperature ranged between 102° and 104.4°F. By the end of the second day the temperature had fallen to 101°F. but the patient still appeared ill, the cough was severe, and there were now signs of consolidation over the right upper lobe. Aureomycin was then started in a dose of 1 Gm. every eight hours. Eight hours after the first dose of aureomycin the patient appeared much better, the temperature had fallen to normal and the cough was less.

This improvement continued throughout the succeeding day. It appeared that this clinical response had occurred too rapidly for it to be attributable directly to an effect of the aureomycin and, therefore, with the patient apparently recovering spontaneously, the drug was discontinued after three doses had been given. However, on the following day the patient's temperature rose again to 100.6°F. and continued to fluctuate between 99° and 102°F. for the next seven days. During this period there was gradual improvement in symptoms and a decrease in extent of pulmonary involvement by physical and x-ray examination. The cold agglutinins, which had been negative on admission, rose to 1:256 nine days later. In retrospect it appears probable that the rapid improvement of the patient following the administration of aureomycin was actually due to the drug, especially since the initial therapeutic response was succeeded by a relapse of the disease soon after treatment was discontinued. The clinical pattern is similar to that of Case II in whom therapy was also stopped too soon.

Case V. (Ward patient, Presbyterian Hospital.) A twenty-seven year old Puerto Rican male was admitted to the hospital on September 26th after thirty-six hours of chilly sensations, non-productive cough and aching pains. On entry his temperature was 103.4°F. and he appeared acutely ill. Apart from this, general physical examination was negative. However, the x-ray on admission showed some patchy pneumonitis in the left mid-lung area. His white count was 11,500 with 74 per cent polymorphonuclears. He was started on intramuscular penicillin, 100,000 units every three hours. The initial sputum was injected into a mouse and a Type XI pneumococcus grew out next day. However, a second specimen two days later was negative for pneumococci.

After forty-eight hours on large doses of penicillin he was worse and the temperature had risen to 105°F. X-ray showed some increase in the pneumonitis. At this time the penicillin was stopped and he was put on aureomycin. His fever declined by fairly rapid lysis, the temperature reaching and remaining normal forty-eight hours after commencement of therapy. (Fig. 4.) Within twenty-four hours, before the temperature was normal, there was a very striking subjective improvement, the patient stating he felt "like a brand new Buick." Cold-agglutinins were negative on September 27th and 30th. On October 7th they had risen to a titer of 1:1024.

This was a young man with an illness of short duration at the time of treatment. Following anreomycin he made a very rapid recovery. There had been no clinical response to forty-eight hours of penicillin therapy. The appearance of cold agglutinins in very high titer leaves no doubt as to the diagnosis.

Case VI. (Patient of Capt. Berté, Fort Totten General Hospital.) The patient was a twenty year old soldier who entered the hospital on September 27th with a two-day history of sore throat, tight cough and feverishness. On admission his temperature was 102°F., pulse rate 120. The temperature curve is illustrated by the accompanying graph (Fig. 5) and during the course of his illness his pulse rate corresponded closely to the height of his fever. He was acutely ill with paroxysmal cough, and rales were noted at both the bases. The admission leukocyte count was 9,300; polymorphonuclears, 72 per cent. Sputum culture showed no pathogens. Urine was negative. X-ray showed a patchy pneumonitis, mainly in the right mid-lung area.

He was started on intramuscular penicillin, 50,000 units every three hours. As can be seen from Figure 5, this treatment had no apparent effect on the fever. By October 1st he was distinctly worse; his cough was almost incessant, more rales were audible over both bases and

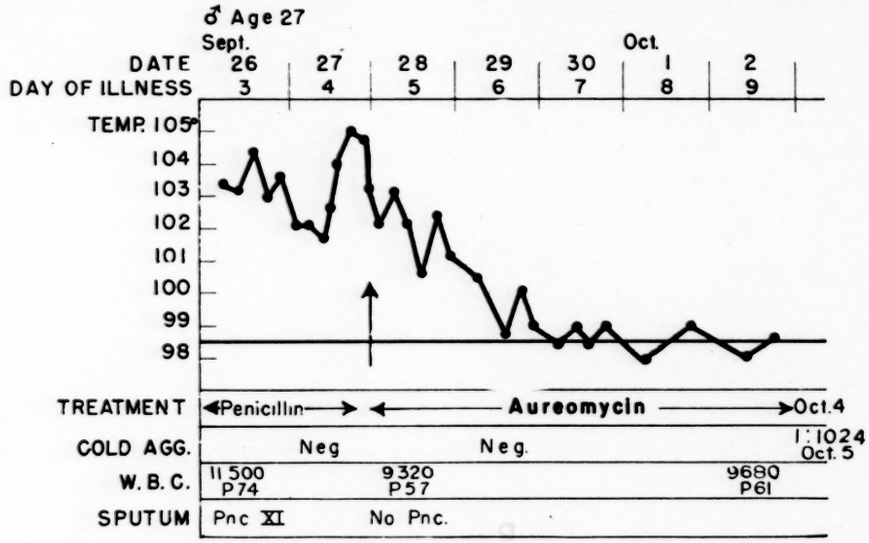


FIG. 4. Chart of Case v.

x-ray showed extension of the pneumonitis to the left lower lobe, with more involvement also on the right. That evening his temperature rose to its highest point, 103°F., and he was started on aureomycin with an initial dose of 1.5 Gm., 1.0 Gm. every six hours to follow on the ensuing day. As can be seen from Figure 5 his temperature fell, reaching and remaining normal forty-eight hours after therapy was instituted. At this time, although he still had considerable cough and many rales were still audible, there was evident general clinical improvement. He received a total of 10.5 Gm. of aureomycin over a four-day period and went on to satisfactory convalescence. During convalescence, however, he developed a mild anemia. The admission hemoglobin had been 13.0 Gm. with 4.85 million red cells. Two weeks later, hemoglobin was found to be 10.5 Gm. with 3.55 million red cells. Three weeks from this date the values rose to higher than the admission level.

Cold agglutinins were negative during the acute phase of the disease but rose to 1:1024 during convalescence. Thus, the diagnosis seems established and improvement followed promptly the institution of aureomycin therapy after a penicillin failure. The significance of the anemia is not clear. In this particular patient, there was some evidence of "Mediterranean Trait" (i.e., racial origin, palpable spleen tip, target cells, and decreased erythrocyte fragility). Wright et al.[5] described anemia occurring in some of their lymphogranuloma venereum patients treated with aureomycin parenterally but believed this was due to the vehicle rather than the drug. It has not been noted in other patients treated orally.

CASE VII. (Patient of Dr. H. Tarnower.) A forty year old white male with fever, cough and malaise, and signs of bilateral pneumonitis was treated at home for eleven days. On the seventh day of his illness a white count was 6,400, with 56 per cent polymorphonuclears. During this period his fever ranged from 99° to 103°F., being mainly around 101°F., and he had an interrupted course of intramuscular penicillin, 300,000 units a day for five days, without effect. On October 1st, the eleventh day of the disease, he was admitted to the hospital. At this time his temperature was 101°F., pulse 84, respirations 20. He appeared acutely but not gravely ill and had a paroxysmal cough. Sputum revealed no pathogens. A chest x-ray at this time showed a patchy pneumonitis in both lower lung fields, more marked on the left. Aureomycin treatment was begun immediately with an initial dose of 1.5 Gm. to be followed by 1.0 Gm. every six hours.

The following day he appeared clinically improved and his temperature was a degree lower. It reached normal forty-eight hours after the commencement of therapy and convales-

cence was uneventful. On the third and fourth hospital days the daily dose of aureomycin was reduced to 3 Gm. and then the drug was discontinued. Cold agglutinins on October 2nd were positive in a titer of 1:128. Chest x-ray on October 9th showed complete clearing of the pneumonitis.

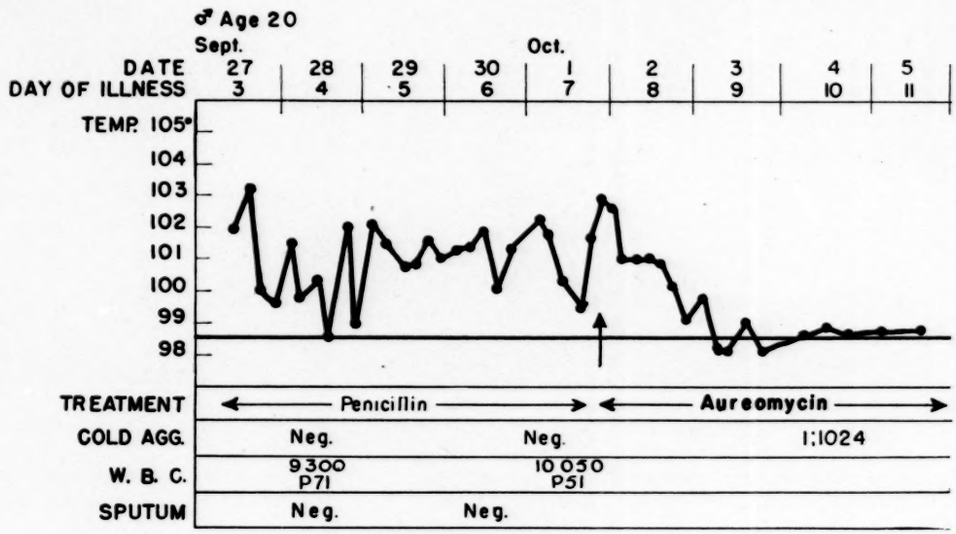


FIG. 5. Chart of Case VI.

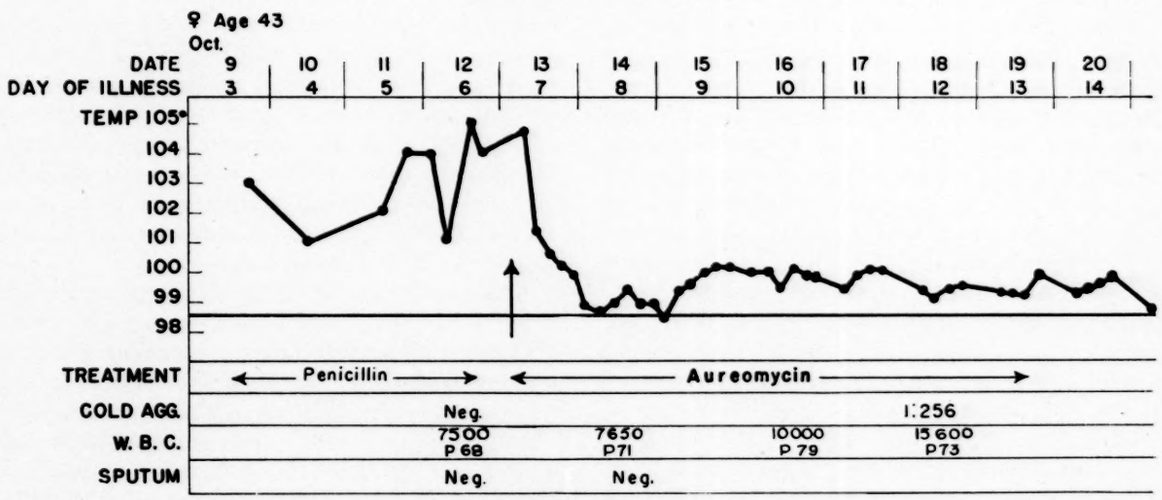


FIG. 6. Chart of Case IX.

This was a rather indolent case of atypical pneumonia, proven by positive cold agglutinins, which seemed to be getting slightly worse at the end of eleven days' treatment with bed rest and penicillin. Following institution of aureomycin therapy rapid clearing of signs and symptoms took place.

CASE VIII. (Patient of Dr. M. Lipkin.) This case will not be presented in detail owing to its complexity and the difficulty of drawing any satisfactory conclusions from it. In brief, a fifty-four year old woman was first seen apparently in extremis after sixteen days of pneumonia which by this time involved both lungs extensively. Cold agglutinins at this time were 1:512 so that the diagnosis seemed established; but as we had not yet treated anyone who had been ill so long or was in such critical condition, aureomycin was given with no very sanguine hope of success. For the next sixteen hours her condition worsened but then took a turn for the better. Slight but definite improvement seemed to be maintained for the ensuing forty hours at the end of which time her temperature was down to 99.2°F.

7 8

FIG. 7. Case IX, film of the chest taken on October 12th, the day treatment was started, shows a band-like density in the right lung, together with some patchy involvement.
FIG. 8. Case IX, x-ray taken three days later; although temperature was down and clinical improvement had taken place, there is little change to be seen in the appearance of the lesion. Five days after this substantial clearing was noted by x-ray.

Unfortunately, this was one of the two cases in which nausea and vomiting were a most unpleasant concomitant of the drug. At this time while out of the oxygen tent for a fairly brief period, the patient went into anoxic collapse with pulmonary edema and apparently both cardiac and respiratory failure. For some hours the situation was desperate but she gradually rallied. Aureomycin was discontinued so as not to re-induce vomiting. For the next four days the problem was one of treating extreme pulmonary insufficiency. Then, on the fifth day following the collapse although her general condition was improved, her temperature began to rise and there was some clinical evidence of reactivation of the pneumonitis. Aureomycin was then started again; this time she tolerated the drug much better and over the ensuing three days her temperature fell and she improved once more. From this point on, recovery from the pneumonia progressed slowly but steadily although a complicating thrombophlebitis occurred in the right leg. Because of the complicated nature of the illness and the interruption in the course of aureomycin therapy, it is impossible to assess the precise role of the drug in her ultimate recovery.

CASE IX. (Patient of Dr. H. B. Wilcox, Jr.) A forty-three year old white housewife with an old history of compensated rheumatic heart disease became ill with sore throat and malaise a week before hospital admission. For four days prior to admission she was under her physician's care at home with temperatures ranging from 101° to 105°F. (Fig. 6.) During this period she developed a racking cough and severe headache, and was treated with penicillin in large doses both intramuscularly and by inhalation, as well as with sulfadiazine, without relief.

On admission she appeared acutely ill and prostrated. Her temperature was 104°F., pulse 100, respirations 24. There were signs of mitral stenosis without evidence of failure. There was some percussion dullness noted over the right chest posteriorly, and slight change in breath sounds, without rales. X-ray revealed the dense, band-like shadow shown in Figure 7. The white blood count was 7,500; polymorphonuclears 62 per cent; urine negative. Sputum showed no pathogens on culture, Streptococcus viridans predominating. She was started on aureomycin at 6 P.M. October 12th, 1.5 gm., 1.0 Gm. every six hours to follow.

The next morning the 8 A.M. temperature was still elevated but the patient stated she felt considerably improved. Her fever declined to 101.4°F. at noon, and then fell still further, reaching normal at 4 A.M. the third hospital day.

It remained normal for a day and then rose a little, hovering between 99° and 100°F. for the next week. This patient was the second in our series to show nausea and vomiting with the drug. These symptoms were distressing to the patient but in all other respects she did extremely well. X-ray taken three days after admission showed very little change in the lesion in spite of her marked clinical improvement. (Fig. 8.) On October 19th, however, there was substantial clearing by X-ray. Cold agglutinins which were negative on admission rose to 1:256 six days later. Thus there was no question as to the diagnosis and it was plain that a remarkable improvement took place after the administration of aureomycin. The drug was continued in varying dosage for one week.

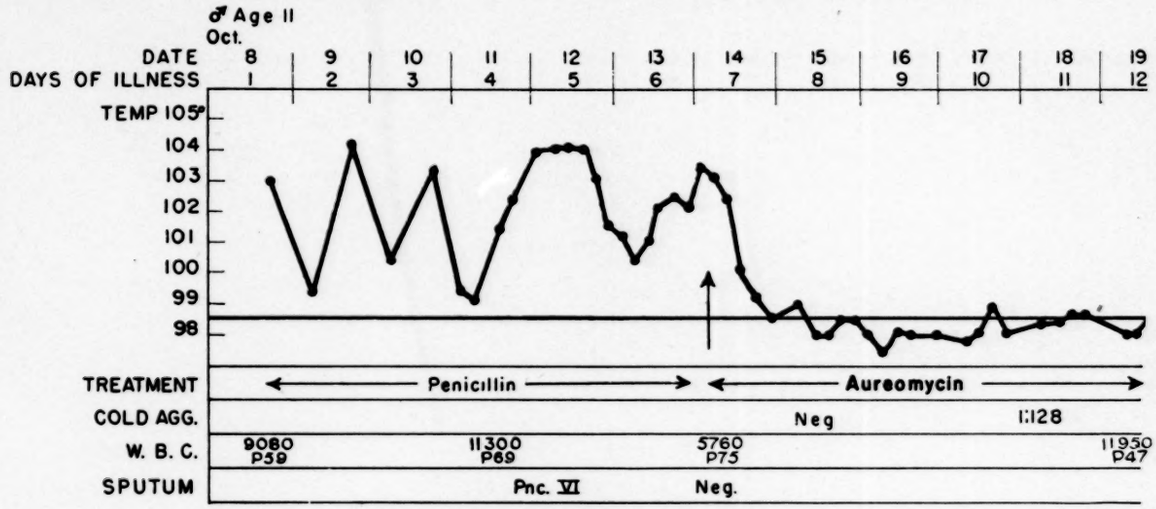


FIG. 9. Chart of Case x.

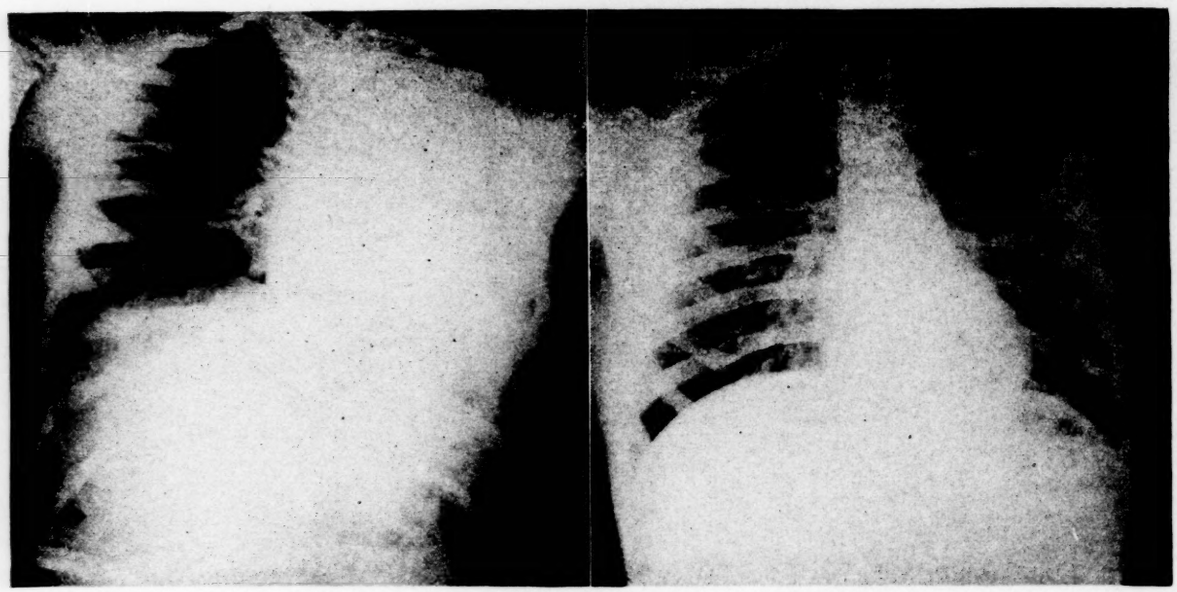
CASE X. (Patient of Dr. Hamilton Southworth.) This patient, the youngest in our series, was an eleven year old white school boy weighing 80 pounds. He became acutely ill on October 8th with malaise, headache and a fever of 103°F. The next day he began to cough and signs of pneumonia appeared at the extreme left base. By October 11th these had progressed to signs of tight consolidation on the left lower lobe. The next day he appeared more toxic and there was evidence of extension of the left upper lobe. The temperature curve during the six days of treatment at home before hospital admission is shown in Figure 9.

On October 9th the white count was 9,080 with 59 per cent polymorphonuclears. On the 12th it was 11,300, with 69 per cent polymorphonuclears, and sputum obtained on this day grew out a type VI pneumococcus. During the whole period, however, he was receiving intramuscular penicillin, 250,000 units twice a day in aqueous solution. This did not appear to influence the progress of the disease and no pneumococci were cultivated from the sputum obtained on hospital admission.

He was admitted at noon on October 13th. Examination disclosed an acutely ill boy, coughing and quite cyanotic. There were signs of dense consolidation of the left upper lobe. Over the lower lobe posteriorly the breath sounds were bronchovesicular, with abundant redux crepitus. There was no detectable displacement of the mediastinal structures. His temperature on admission was 102.2°F. After x-ray he was immediately given 0.8 Gm. of aureomycin and placed in oxygen.

His admission white count was 8,760 with 75 per cent polymorphonuclears. X-ray (Fig. 10) showed a complete density occupying the left lung field. From a radiologic point of view there was some indication of atelectasis but the physical findings were those of consolidation.

As indicated in Figure 9, his temperature fell promptly, reaching normal in twelve hours, where it remained thereafter. There was rapid defervescence of the physical signs of pneumonia and a striking relief of all symptoms. He was maintained on aureomycin for five days, dosage being scaled down from 0.6 Gm. every six hours to 0.3 Gm. (his body weight being about 80 pounds). Repeat x-ray, five days after admission, showed complete clearing of the lesion. (Fig. 11.) Cold agglutinins which were negative on October 14th rose to 1:128 four days later, the eleventh day of disease.



10 11

FIG. 10. Case x, x-ray taken on October 14th shows massive involvement of left lung.
FIG. 11. Case x, five days later the lesion has disappeared.

It may be objected that the x-ray and physical signs in this case were most unusual for atypical pneumonia. Moreover, a type VI pneumococcus was isolated from the sputum on one occasion. On the other hand, lobar densities have been described in atypical pneumonia and we believe that the low white count, the failure to respond to penicillin in adequate dosage and the sharp rise in titer of cold agglutinins establish the diagnosis.

SUMMARY AND CONCLUSIONS

1. Ten patients with what we believe to be atypical ("virus") pneumonia have been treated with aureomycin orally. Of these eight showed the development of cold agglutinins at the expected period in the disease.

2. In nine patients the temperature became normal twelve to forty-eight hours after the drug was first administered, with corresponding improvement in their general condition. In two of these treatment was discontinued at this time, and what appeared to be a recrudescence of the disease took place. In the other seven cases treatment was maintained and uneventful recovery ensued.

3. One patient, a fifty-four year old woman who appeared in extremis at the time treatment was initiated, ultimately recovered but we do not feel justified in drawing any conclusions as to the effect of the drug in her case.

4. No important toxic side effects of the aureomycin were noted.

5. The data submitted in this report suggest that aureomycin may have an antiviral effect against the agent which causes atypical pneumonia in man.*

REFERENCES

1. DUGGAR, B. M. *Proc. N. Y. Acad. Sc.*, in press.
2. HARNED, B. K., CUNNINGHAM, R. W., CLARK, M. C., COSGROVE, R., HINE, C. H., MCCAULEY, W. J., STOKEY, E., VESSEY, R. E., YULA, N. N. and SUBBAROW, Y. (In press.)
3. WONG, S. C. and COX, H. (In press.)
4. BRYER, M. S., SCHOENBACH, E. B., CHANDLER, C. A., BLISS, E. A. and LONG, P. H. Aureomycin, experimental and clinical investigations. *J. A. M. A.*, 138: 117, 1948.
5. WRIGHT, L. T., SANDERS, M., LOGAN, M. A., PRIGOT, A. and HILL, L. M. Aureomycin: a new antibiotic with virucidal properties. *J. A. M. A.*, 138: 408, 1948.

* Since this report was submitted, five additional patients with atypical pneumonia have been given aureomycin treatment with very satisfactory results.

Pheochromocytoma with Diabetes and Hypertension*

Report of Two Cases Cured by Operation

A. DE VRIES, M.D., M. RACHMILEWITZ, M.D. *and* M. SCHUMERT, M.D.
Jerusalem, Palestine

THE characteristic manifestations of pheochromocytoma are paroxysms of hypertension accompanied by headache, palpitation, perspiration, nausea and occasional vomiting. In exceptional cases persistent hypertension has been observed. Occasionally paroxysmal hyperglycemia and glycosuria also have been found. All these signs and symptoms of the disease have disappeared in successfully operated cases, even in those in which the clinical picture resembled that of malignant hypertension. Persistent hyperglycemia and glycosuria associated with pheochromocytoma which disappeared after operation has been described by Duncan et al.[1] and by Green.[2]

The present report is concerned with two cases of pheochromocytoma, in one of which paroxysmal hypertension and paroxysmal glycosuria were notable features while in the other paroxysmal hypertension and persistent diabetes existed. In both, disappearance of all signs and symptoms followed removal of the tumor.

CASE REPORTS

CASE I. J. J., a forty-one year merchant, was admitted to the Hadassah Hospital on April 4, 1946, complaining of attacks of headache, pain in the precordial region, palpitation, dizziness and profuse perspiration. At the age of twenty-four he contracted syphilis and was treated with salvarsan. Subsequently, repeated blood examinations for lues were negative. In 1941 his blood pressure was found to be 160/90 mm. Hg. In the same year he suffered an attack of anginal pain; the blood pressure at that time was 160/100 mm. Hg. The same blood pressure was noted again in May, 1945. In June, 1945 he had a severe attack of pain in the chest, radiating to the left arm, accompanied by perspiration, dizziness and palpitation. He was admitted to a hospital where the diagnosis of myocardial infarction was made and which was confirmed by electrocardiographic examination. During his three months' stay in that hospital he had repeated attacks of cardiac pain with headache and perspiration during which systolic blood pressure readings of 200 mm. Hg were registered; after the attacks the blood pressure returned to normal. In October, 1945 he was transferred to another hospital where he was confined to bed for about five months with complaints of anginal pain, headache, sleeplessness and constipation. He also had frequent attacks of severe headache with tinnitus, dizziness and profuse perspiration accompanied by waves of heat in the face. The blood pressure fluctuated between normal levels and 200/130 mm. Hg during the attacks. The urine contained a small amount of albumin, sugar up to 5.7 per cent and occasional traces of acetone. The blood sugar was elevated, the highest values being 400 mg. per cent; 40 to 80 units of regular insulin were needed to control the diabetes. On the basis of these findings a tentative diagnosis of tumor of the adrenal medulla was made but kidney x-rays were not confirmatory. After leaving the hospital his condition grew worse and he was admitted to our hospital in April, 1946 because of aggravation of his diabetic condition.

* From The Department of Internal Medicine, Division B, The Hadassah Rothschild University Hospital, Jerusalem, Palestine.

On admission the nutritional state was found to be poor. The patient was restless, perspired profusely and had an acetone breath. The color of his face was strikingly red, there was no peripheral edema and no abnormal pigmentation of the skin. The pulse was 100 and regular. The heart was found slightly enlarged to the left; there were no signs of congestive failure. Examination of the abdomen was negative. The blood pressure was 200/140 mm. Hg. The urine contained a moderate amount of albumin and a large quantity of sugar and acetone. The blood sugar was 400 mg. per cent. The patient was given 100 units of regular insulin during the first twenty-four hours, after which the acetonuria disappeared and the blood sugar came down to 260 mg. per 100 cc.

During his stay in the hospital the patient complained of weakness, severe headache and dull precordial pain, palpitation, dizziness, bursting headache, tinnitus and severe perspiration. The blood pressure showed marked fluctuations. The slightest excitement, even application of the blood pressure cuff, would provoke a rise in blood pressure up to levels of 200/140 at which it sometimes remained a few minutes only to fall suddenly to very low levels (80/60 mm. Hg). Profuse perspiration appeared constantly whenever the blood pressure fell. The paroxysms appeared quite irregularly. Occasionally they appeared repeatedly during a single day, at other times there were intervals when there were no particular subjective complaints and the blood pressure was constantly normal.

Fasting blood sugar values varied from 120 to 260 mg. per cent. Following admission, on a diet containing 120 Gm. of carbohydrate, 60 to 90 Gm. of sugar were excreted daily. On 80 units of insulin daily, glucose tolerance was improved and the diabetes was controlled; the carbohydrate intake was increased to 200 Gm. a day. Frequent blood sugar determinations during the paroxysms of hypertension revealed values varying from 130 to 230 mg. per cent. In paroxysm-free intervals of several days' duration the severity of the diabetes did not change and the same amount of insulin had to be given.

Other laboratory findings revealed the following: Blood: hemoglobin, 15.5 Gm. per cent; red cells, 5,250,000 to 5,900,000/mm.;[3] packed red cell volume, 43 to 52 per cent; leukocytes, 12,000 to 15,600/mm.[3] Sedimentation rate, 17 hours (Linzenmeier's method). Blood urea, 28 mg. per cent; cholesterol, 450 mg. per cent. Kidney function: urea-clearance, 55 per cent (standard clearance test of van Slyke). Eye fundi: narrowing of the arteries, fluctuations in caliber; increased light reflex, arteriovenous compression, hemorrhages. Electrocardiogram: left axis deviation; T_1 and T_2 isoelectric; T_3 slightly positive, T_4 negative.

The unusual fluctuations of blood pressure, attacks of perspiration, the throbbing headache and palpitation and the disturbance in the carbohydrate metabolism were compatible with the diagnosis of tumor of the suprarenal medulla. The following procedures were undertaken to verify the diagnosis: Pressure on the loins: the effect was not conclusive; there was a rise in blood pressure from 110/80 to 160/115 mm. Hg, but it occurred after pressure on the right as well as on the left side. Cold pressor test: the blood pressure rose from 130/100 to 220/150 mm. Hg.

Histamine test (Roth and Kvale):[3] after the intravenous injection of 0.075 mg. of histamine hydrochloride the blood pressure rose from 130/100 to 250/170 mm. Hg, lasted ten minutes and, at the same time, the patient experienced the complaints usually felt during the paroxysms, even to an increased degree.

X-rays of the kidneys: after intravenous pyelography both kidneys appeared normal in position and size. The pelvis and calices were not distorted and no shadows were seen in the suprarenal region. Planigraphy revealed a normal left kidney; the upper border of the right kidney was not sharply visualized in the various sections.

Because of the latter finding and the fact that tumors of the adrenal medulla occur more frequently on the right side than on the left, the right side was explored on May 13, 1946, by Professor F. Mandl. A tumor of tangerine size was found in the region of the right adrenal gland and removed.

The following observations were made during and immediately after the operation: With the institution of ether anesthesia, the blood pressure rose from 130/100 to 200/150 mm. Hg. Manual pressure on the tumor *in situ* raised the blood pressure to 250/160 mm. Hg. Later, at the time of ligation of the blood vessels, it rose to 300/190. Immediately after removal of the tumor the blood pressure fell to 120/90 and then to 95/80. After 0.25 mg. of epinephrine intravenously and two ampules of supracort intramuscularly the blood pressure rose to 170/130 for a

few minutes and then came down to 115/90. Ten minutes after the operation the patient suddenly went into shock and the blood pressure fell to zero; 0.05 Gm. of ephedrine administered intravenously raised the blood pressure to 100/75. During the day of the operation an intravenous infusion of saline and isotonic glucose was instituted with a total amount of 0.6 Gm. ephedrine. In addition four ampules of supracort were given intramuscularly. The blood pressure was stabilized at 110/80.

Together with the glucose, insulin was administered during the day of the operation and the day after in a total amount of 90 units. During this period the blood sugar fluctuated between 150 to 230 mg. per cent and then became normal at which point it remained while the patient was on a normal diet without insulin.

The pathologic report disclosed the following: Macroscopic examination revealed that the specimen consisted of a rounded, slightly elongated body about 3 by 4 by 6 cm. in size and 30 Gm. in weight. In its greater part it was covered by a thin, transparent, fibrous capsule. In one place the capsule was torn and a friable mass of brown-reddish color protruded from underneath. The intact surface of the specimen was studded with nodular elevations of variable size. Cut surface revealed the greatest part of the specimen to be composed of the same friable and disintegrated mass just mentioned which could be removed with ease, thus leaving a large cystic space. The remaining tissue was a uniformly dark reddish-brown color. At one pole of the specimen there was a portion of bright yellow tissue which could be easily separated; it presented the aspect of a round normal adrenal cortex but on cross section no typical medulla could be detected.

Microscopic examination showed that the tissue in the solid portion of the tumor was composed of large epithelium-like cells which lay within a stroma consisting of thin-walled blood vessels and capillaries and only sparse argentophile fibers which extended from the adventitia of some of these vessels. The large cells formed densely packed sheets and adjacent to some blood vessels they were found in palisade arrangement converging toward the vessel. The cells were fairly uniform with a clear eccentric nucleus. The cytoplasm was palely eosinophilic and granular. There were scattered foci of necrosis which contained scattered nuclear fragments. In the vicinity of the cystic interior of the tumor such necrotic foci were fused together over wide areas. Sections of material after fixation in Mueller's fluid: a diffuse brown stain was prominent in the necrotic areas in the wall of blood vessels and in the cytoplasm of a great number of large vacuolated cells. A section from the adrenal gland adjacent to but separated from the tumor showed the cortex to be regularly built with extensive hemorrhage in the reticulate zone. In place of the medulla chromaffine cells could be distinguished with certainty. There were a number of small round cells with dark nuclei; the central vein was thin-walled in all sections, an isolated bundle of nerve fibers was also seen.

Histological diagnosis: Chromaffine tumor of adrenal medulla.

The adrenalin content of the tumor was determined as follows: A sample of the tumor was extracted with 10 per cent trichloroacetic acid about twenty minutes after extirpation and aliquot portions of the extract were analyzed by the chemical photometric method of Barker et al.[4] The value obtained, 13 mg. per Gm. tissue, appeared so high that it was decided to repeat the analyses by a biologic method in view of some uncertainty concerning the specificity of the chemical method. In a preliminary experiment the presence of a highly active pressor substance in the extract was confirmed by the rise in blood pressure of a rabbit in urethane narcosis after intravenous injection of an amount of the extract corresponding to about 0.22 mg. adrenalin (calculated from the chemical determination). The quantitative assay was carried out on the isolated intestine[5] using rat ileum instead of the rabbit ileum of the original method. By comparison with an adrenalin standard the content of the tumor was calculated to be about 7 mg. per Gm., i.e., about one-half that obtained by the chemical method. The total adrenalin content of the tumor weighing 30 Gm. was between 210 to 390 mg. as compared with 3 to 9 mg. of adrenalin in normal human adrenals. The identity of the active substance in the extract was confirmed by the abolition of its action on the intestine by previous addition of ergotoxin. Ergotoxin, 100γ, abolished the relaxing effect of 1γ of adrenalin on the isolated rat intestine in a 50 cc. bath. Postoperative complications were pneumothorax on the right side which required removal of air by puncture once, thrombophlebitis of the left leg

and three pulmonary infarctions, twice in the left and once in the right lung. The effects of the operation on the manifestations of the disease are summarized in Table 1.

Comment. This patient was a man of forty-one suffering from attacks of headache, chest pain, palpitation, perspiration, dizziness and tinnitus. There were frequent paroxysms of hypertension, the blood pressure between the attacks being normal. In addition severe persistent diabetes was present which required 80 units of regular insulin. The diagnosis of tumor of the adrenal medulla was made and confirmed by operation. After removal of the tumor the diabetes and paroxysmal hypertension disappeared. Histologic examination showed a chromaffine tumor of the adrenal medulla which weighed 30 Gm. and contained 7 mg. of adrenalin per Gm. of wet tissue.

TABLE 1

Case 1	Before Operation	After Operation
Blood pressure: mm. Hg		
Spontaneous variations	80/60–200/140	110/80–135/90
Cold pressor test	220/150	170/140
Histamine test (0.075 mg. histamine hydrochloride intravenously)	250/170	
Ocular fundi	Narrow arteries, fluctuations in caliber, increased reflexes arteriovenous compression, hemorrhages; a large hemorrhage near the disc	Slight constriction of arterioles; in some places irregularity of caliber
Kidney:		
Urine: albumin	1+	Negative
Function: urea clearance (standard)	55 per cent	60 per cent
Electrocardiogram	T_1 and T_2 isoelectric; T_3 slightly positive; T_4 negative	1½ months after operation: higher voltage than before; T_1 isoelectric, T_2 slightly positive; 2½ months after operation: higher T_1 slightly positive; T_2, T_3 and T_4 positive
Blood:		
Hemoglobin	15.5 Gm. per cent	13.2 Gm. per cent
Hematocrit	43–52 per cent	39 per cent
Red cell count	5.25–5.90 millions/mm.^{3}	4.0 millions/mm.^{3}
White cell count	12,000–15,600/mm.^{3}	7,000/mm.^{3}
Sedimentation rate (Linzenmeier)	17 hr.	3¾ hr.
Blood sugar tolerance curve		Fasting: 73 mg. per cent
Ingestion of 60 Gm. glucose		½ hr. after ingestion 126 mg. per cent 1 hr. after ingestion 156 mg. per cent 1½ hr. after ingestion 129 mg. per cent 2 hr. after ingestion 92 mg. per cent 2½ hr. after ingestion 66 mg. per cent
Effect of 0.5 mg. epinephrine subcutaneously on blood pressure		initial level 130/90 mm. Hg 1–2 min. after injection 140/100 mm. Hg 4 min. after injection 125/90 mm. Hg
Blood sugar		initial level 87 mg. per cent 15 min. after injection 83 mg. per cent 30 min. after injection 98 mg. per cent 50 min. after injection 119 mg. per cent 70 min. after injection 138 mg. per cent 90 min. after injection 128 mg. per cent

CASE II. R. S., a thirty-three year old man whose case was reported in detail elsewhere,[6] presented the following clinical features: the first symptoms referable to the disease, consisting of attacks of perspiration, started seven years before it was recognized. During the six months prior to the operation attacks of hypertension were observed, the blood pressure rising sometimes to 250/180 mm. Hg. The clinical picture resembled that of malignant hypertension with diffuse, severe vascular changes; the ocular fundi showed the findings typical of hypertensive neuroretinopathy: papilledema, constricted arterioles, with arteriovenous compression, multiple retinal hemorrhages and exudates. The heart was markedly enlarged to the left; the electrocardiogram showed evidence of myocardial damage and coronary artery disease. During the attacks paroxysms of cardiac asthma and pulmonary edema occurred repeatedly. There was also evidence of renal involvement, manifested by albuminuria, reduced concentration capacity and lowered urea clearance test (47 per cent standard clearance). The urine occasionally contained small amounts of sugar. The blood sugar level fluctuated from normal to increased values (300 mg. per cent) obtained during the paroxysms of hypertension. However, once a blood sugar value of 218 mg. per cent was found when the blood pressure was normal. Blood cholesterol was 400 mg. per cent.

A tangerine-sized tumor, removed from the right adrenal region, showed histologically the characteristic features of pheochromocytoma. The adrenalin content of this tumor which weighed 95 Gm. was 2 mg. per Gm. wet tissue.

Following operation, the paroxysms of hypertension disappeared together with the signs of heart failure. The fundal changes regressed rapidly and the papilledema disappeared completely within one month of the operation. At the same time the hemorrhages were resorbed. Narrowing of the retinal arteries has persisted for over one and one-half years. There has been marked improvement in the kidney function. Six months after the operation the concentration capacity was normal and the urea clearance rose from 47 to 72 per cent. The albuminuria disappeared. The glycosuria and hyperglycemia disappeared completely immediately after the operation and the blood sugar tolerance curve showed normal values five weeks after the operation. The blood cholesterol concentration became normal.

Comment. This thirty-three year old male suffered from attacks of perspiration, headache, palpitation, severe dyspnea and paroxysmal hypertension. Severe visual disturbance was present and the ocular fundi showed the findings typical of malignant hypertension. Hyperglycemia and glycosuria occurred, generally coincident with the paroxysms of hypertension. Removal of a tumor of the right adrenal medulla resulted in almost complete restoration to normal.

COMMENTS

In the second case the clinical signs were more characteristic than in the first. Both the hypertension and hyperglycemia were paroxysmal in nature. Although there was no strict relationship between the height of the hypertension and blood sugar level, the highest blood sugar figures were obtained during the paroxysms of hypertension. It is noteworthy that in this case, although normal blood pressure levels were registered during long intervals between the attacks, there were diffuse vascular changes resembling those found in the malignant phase of persistent hypertension. It might be expected that these vascular changes, presumably lasting for many years and also affecting the kidneys, would cause sustained hypertension even after removal of the tumor. This was not the case and except for arteriosclerotic changes in the ocular fundi the evidence of generalized vascular disease disappeared after operation and the blood pressure remained permanently normal.

In Case I the paroxysms of hypertension were usually very short, sometimes lasting for a few minutes only, and there were many days when a rise in blood pressure did not occur at all. At times different blood pressure readings were registered in rapid succession. The increased perspiration was not synchronous with the elevation of the blood pressure but usually appeared when the blood pressure re-attained normal levels. Although the hypertensive seizures were of short duration, there was definite evidence

of widespread vascular sclerosis as manifested by retinal changes and cardiac and renal involvement. In this case operation resulted in marked improvement.

The disturbance of carbohydrate metabolism in this case is of particular interest. Here we are not dealing with paroxysmal hyperglycemia as in Case II but with a type of diabetes indistinguishable from ordinary diabetes. The metabolic disturbance was at times so severe that it constituted the principal clinical feature of the disease. It was then accompanied by severe acidosis, very high blood sugar levels (up to 400 mg. per cent) and glycosuria amounting to 60 to 80 Gm. a day, a condition which required large amounts of insulin. After operation all the signs of diabetes disappeared almost immediately. That excessive amounts of epinephrine were responsible for the diabetes and that no permanent damage was present in the pancreas is well demonstrated by the normal blood sugar tolerance curve obtained two and one-half months after operation.

These observations raise many intriguing questions. Although the action of epinephrine on the circulatory system and on carbohydrate metabolism has been the subject of numerous investigations, the clinical features of pheochromocytoma are still poorly understood. The lack of correlation between hyperglycemia and hypertension in pheochromocytoma is striking. Hypertension, usually paroxysmal and rarely persistent,[7] is a constant feature in pheochromocytoma. Hyperglycemia, however, is frequently absent. Of fifty reported cases, including our own two cases of pheochromocytoma, in which blood and urinary sugar were studied evidence of transient hyperglycemia and glycosuria was present in twenty-one. In twenty-four cases no disturbance of carbohydrate metabolism was found. In five individuals (including our patient in Case I) permanent diabetes was present; three of these patients (including our Case I) came to operation with resultant complete cure of the diabetes.

A time relationship between hypertension and hyperglycemia was frequently observed. In some cases, as in our Case II, paroxysms of hypertension coincided with hyperglycemia. Occasionally excessive blood pressure rises were associated only with moderate hyperglycemia or none at all. Perhaps serial blood sugar determinations would have shown a later rise in blood sugar as it is known that after the intravenous injection of epinephrine hyperglycemia appears somewhat later than the rise in blood pressure.[10] It is remarkable that in the case reported by Thorn et al.,[7] in which persistent hypertension was present for seven years, careful study failed to reveal any diabetic disturbance. On the contrary a flat blood sugar tolerance curve was found.

In cases of pheochromocytoma epinephrine is being produced in excessive amounts. As to its release into the circulation and the factors influencing it no definite facts are available. From the finding of Beer et al.[11] and others[12,13] it follows that the hypertensive paroxysm is associated with hyperadrenalinemia. The degree of hyperadrenalinemia found by various investigators during the hypertensive crises of pheochromocytoma shows considerable variation in the few instances in which it was examined. The lack of unanimity may possibly be explained by differences in the methods used for the estimation of blood epinephrine.[11–13] There are also insufficient data as to the amount of epinephrine circulating in the blood between the attacks. Stroembeck and Hedberg[12] in their case found a 1,000-fold increase in blood epinephrine during the paroxysms and a 30-fold increase between the attacks. On the other hand, Espersen and Dahl-Iversen[13] using a different method found a 4- to 5-fold increase in blood epinephrine during an attack whereas between attacks the epinephrine content was normal or even subnormal. From clinical observations it is known that certain movements and pressure on the kidney region may bring about a hypertensive paroxysm in pheochromocytoma, presumably by producing an increased outpouring of epinephrine. On this basis transient

hypertension and hyperglycemia are easily understood. It is not clear, however, why hyperglycemia is not as constant a feature of pheochromocytoma as the paroxysm of hypertension, especially considering the fact that in animals as well as in man the minimal amount of epinephrine necessary to produce hyperglycemia does not provoke a rise in blood pressure.[14–17]

The explanation of persistent diabetes in some cases of pheochromocytoma and of persistent hypertension in others meets with still more difficulties. It has not been possible to produce persistent diabetes or persistent hypertension in animals by continuous administration of epinephrine. Under such conditions the elevated blood sugar and blood pressure begin to decline.[18–20] The explanation offered for this is a reflex overproduction of insulin and depression of epinephrine secretion of the suprarenal gland.[20,21] Another factor may be an increased rate of destruction of the epinephrine injected.[22] The theory of suppressed epinephrine secretion is supported by the excessive drop in blood pressure observed in all cases of pheochromocytoma immediately after removal of the tumor and by the subnormal resting values found in Case 1 (80/60 mm. Hg).

In the two cases with persistent diabetes reported by McCullagh et al.[8] and by Rogers[9] the resting blood pressure was found to be elevated and to rise to excessively high levels during the paroxysms. It might be assumed that in these cases a continuous excessive secretion of epinephrine took place, producing persisten-hyperglycemia and hypertension. The possibility that continuous excessive secretion of epinephrine took place in Case 1 of out series is not warranted by the behavior of the blood pressure. In this patient the hypertension was definitely paroxysmal, the intervening blood pressure even being subnormal while the diabetes was permanently present. This discrepancy cannot be explained by the assumption that disease of the pancreas was responsible since after the operation the signs of diabetes disappeared completely and a normal blood sugar tolerance curve was obtained. Since the presence of the hypophysis is necessary for the production of hyperglycemia by epinephrine,[23–26] one might assume that in this case sustained hyperactivity of the anterior lobe of the hypophysis is induced by the hyperadrenalinemia and that this hyperactivity is abolished when the source of the hyperadrenalinemia is removed. Two additional features observed in Case 1 are of interest: the acidosis and the good response to insulin. This patient was admitted to the hospital in a state of severe acidosis with acetonuria. Acetonuria has also been observed in animals receiving epinephrine.[27] In pancreatic diabetes ketosis is explained by an overproduction of ketone bodies in a liver depleted of glycogen, consequent to lack of insulin. In epinephrine diabetes, however, there is no glycogen depletion in the liver. On the contrary, after a short interval following epinephrine injection liver glycogen increases.[28–30] Epinephrine induces the muscles to produce an increased amount of lactic acid which is transported by the blood stream to the liver where it is converted to glycogen.[31] This process balances and actually supersedes the glycolytic action of epinephrine on the liver, the net result being hyperglycemia, decrease of muscle glycogen and increase of liver glycogen. Therefore, development of ketosis in pheochromocytoma is difficult to explain except in case of severe depletion of muscle glycogen or if it is assumed that epinephrine accelerates fat catabolism, by direct action in this respect.[32–36]

The severe diabetes of the first patient before operation was well controlled by insulin. This conforms with the observed antagonism between insulin and epinephrine in animals[37–39] as well as in perfused organs.[40–41]

SUMMARY

Two cases of pheochromocytoma have been reported. One patient had paroxysmal hypertension and persistent diabetes while in the other patient both hypertension and

diabetes were paroxysmal. In both patients a complete cure was effected by removal of the adrenal medullary tumor. The inconsistency of the symptomatology of pheochromocytoma with the known physiologic and biochemical effects of epinephrine has been pointed out.

REFERENCES

1. Duncan, L. E., Jr., Semans, J. H. and Howard, J. E. Adrenal medullary tumor (pheochromocytoma) and diabetes mellitus: disappearance of diabetes after removal of the tumor. *Ann. Int. Med.*, 20: 815, 1944.
2. Green, D. M. Pheochromocytoma and chronic hypertension. *J. A. M. A.*, 131: 1260–1264, 1946.
3. Roth, G. M. and Kvale, W. F. Tentative test for diagnosis of pheochromocytoma. *J. Lab. & Clin. Med.*, 30: 366–368, 1945.
4. Barker, J. H., Eastland, C. J. and Evers, N. The colorimetric determination of adrenaline in suprarenal gland. *Biochem. J.*, 26: 2129–2143, 1932.
5. Burn, J. H. Methods of Biological Assay. London, 1928. Oxford University Press.
6. Vries, de A., Mandl, F., Rachmilewitz, M. and Unger, H. Paroxysmal hypertension due to adrenal medullary tumor (pheochromocytoma). Successful operation. *Surgery*, 19: 522–529, 1946.
7. Thorn, G. W., Hindle, J. A. and Sandmeyer, J. A. Pheochromocytoma of adrenal associated with persistent hypertension: case report. *Ann. Int. Med.*, 21: 122–130, 1944.
8. McCullagh, E. P. and Engel, W. J. Pheochromocytoma and hypermetabolism: report of 2 cases. *Ann. Surg.*, 116: 61–75, 1942.
9. Rogers, E. Paroxysmal hypertension associated with a ganglioneuroma of the suprarenal medulla. *Am. Heart J.*, 8: 269–274, 1932.
10. Cori, C. F. Mammalian carbohydrate metabolism. *Physiol. Rev.*, 11: 143–276, 1931.
11. Beer, E., King, F. H. and Prinzmetal, M. Pheochromocytoma with demonstration of pressor (adrenaline) substance in blood preoperatively during hypertensive crises. *Ann. Surg.*, 106: 85–97, 1937.
12. Strombeck, J. P. and Hedberg, T. P. Tumor of suprarenal medulla associated with paroxysmal hypertension. Report of case preoperatively diagnosed and cured by extirpation after capsular incision. *Acta chir. Scandinav.*, 82: 177–189, 1939.
13. Espersen, T. and Dahl-Iversen, E. The clinical picture and treatment of pheochromocytoma of the suprarenal. Two own cases with paroxysmal hypertension, improved by treatment with methylthiouracil and cured by surgical intervention. *Acta chir. Scandinav.*, 94: 271–290, 1946.
14. Cori, C. F. and Buchwald, K. W. Effect of continuous intravenous injection of epinephrine on the carbohydrate metabolism, basal metabolism and vascular system of normal men. *Am. J. Physiol.*, 95: 71–78, 1930.
15. Trendelenburg, P. and Fleischauer, K. Ueber den Einflusz des Zuckerstiches auf die Adrenalin Sekretion der Nebennieren. *Ztschr. f. d. ges. exper. Med.*, 1: 369–396, 1913.
16. Cori, C. F., Cori, G. T. and Buchwald, K. W. The mechanism of epinephrine action. Changes in blood sugar, lactic acid and blood pressure during continuous intravenous injection of epinephrine. *Am. J. Physiol.*, 93: 273–283, 1930.
17. Cori, C. F. and Cori, G. T. The influence of constant intravenous injection of epinephrine on blood sugar of rats. *Proc. Soc. Exper. Biol. & Med.*, 27: 560–561, 1930.
18. Cori, C. F., Fisher, R. E. and Cori, G. T. The effect of epinephrine on arterial and venous plasma sugar and bloodflow in dogs and cats. *Am. J. Physiol.*, 114: 53–68, 1935.
19. Mylon, E., Cashman, C. W. and Winternitz, M. C. The relation of adrenalin and of the carotid sinus to the hyperglycemia of shock. *Am. J. Physiol.*, 142: 638–647, 1944.
20. Malmejac, J. and Donnet, V. Sur les variations de la glycemie au cours d' injections intraveineuses continués de petites doses d'adrenaline. *Compt. rend. Soc. de Biol.*, 119: 734–736, 1935.
21. Malmejac, J., Donnet, V. and Desanti, E. Injection continué d'adrenaline et adrenaline-secretion. *Compt. rend. Soc. de Biol.*, 119: 1152–1154, 1935.
22. Herman, H., Morin, G. and Vial, J. Sur l'action vaso-motrice des doses infimes d'adrenaline. *Compt. rend. Soc. de Biol.*, 122: 1099–1101, 1936.
23. Aschner, B. Ueber die Funktion der Hypophyse. *Pflüger's Arch. f. d. ges. Physiol.*, 146: 1–146, 1912.
24. Corkill, A. B., Marks, H. P. and White, W. E. Relation of the pituitary gland to the action of insulin and adrenalin. *J. Physiol.*, 80: 193–205, 1933.
25. Cope, O. and Marks, H. P. Further experiments on the relation of the pituitary gland to the action of insulin and adrenaline. *J. Physiol.*, 83: 157–176, 1934.
26. DeBodo, R. C., Block, H. I. and Gross, I. H. Role of anterior pituitary in adrenaline hyperglycemia and liver glycogenolysis. *Am. J. Physiol.*, 137: 124–135, 1942.
27. Anderson, A. B. and Anderson, M. D. The effect of adrenaline on ketosis in phloridzinised and normal rats. *Biochem. J.*, 21: 1398–1403, 1927.
28. Sahyun, M. and Luck, J. M. The influence of epinephrine and insulin on the distribution of glycogen in rabbits. *J. Biol. Chem.*, 85: 1–20, 1929.
29. Cori, C. F. and Cori, G. T. Mechanisms of epinephrine action: influence of epinephrine on carbohydrate metabolism of fasting rats, with note on new formation of carbohydrates. *J. Biol. Chem.*, 79: 309–319, 1928.
30. Cori, C. F. and Cori, G. T. Mechanism of epinephrine action: influence of epinephrine on utilization of absorbed glucose. *J. Biol. Chem.*, 79: 343–355, 1928.
31. Cori, C. F. and Cori, G. T. Glycogen formation in the liver from d- and l-lactic acid. *J. Biol. Chem.*, 81: 389–403, 1929.
32. Boothby, W. M. and Sandiford, I. The calorigenic action of adrenalin chlorid. *Am. J. Physiol.*, 66: 93–123, 1923.
33. Dontcheff, L. and Schaeffer, G. Evolution de

l'extra chaleur de l'action dynamique specifique des protides chez le lapin a la neutralité thermique et a basse temperature. *Compt. rend. Soc. de Biol.*, 127: 1290–1293, 1938.

34. Dontcheff, L. and Schaeffer, G., Les protides ne sont pas utilisés dans la thermogenese reflexe de rechauffement. *Compt. rend. Soc. de Biol.*, 127: 1294–1295, 1938.
35. Neufeld, A. H. and Ross, W. D. Blood ketone bodies in relation to carbohydrate metabolism in muscular exercise. *Am. J. Physiol.*, 138: 747–752, 1943.
36. Blixenkrone-Moller, N. Respiratorischer Stoffwechsel und Ketonbildung der Leber. *Ztschr. f. physiol. Chem.*, 252: 117–136, 1938.
37. Issekutz, B. von. Beitraege zur Wirkung des Insulins. I. Mitteilung: Zuckerbildung der ueberlebenden Froschleber. *Biochem. Ztschr.* 147: 264–274, 1927.
38. Nayer, P. P. De l'equilibre insuline-adrenaline. *Compt. rend. Soc. de Biol.*, 111: 1049–1051, 1932.
39. Bouckaert, J. P. and De Duve. The action of insulin. *Physiol. Rev.*, 27: 39–71, 1947.
40. Issekutz, B. von. Beitraege zur Wirkung des Insulins. II. Mitteilung: Insulin-Adrenalin Antagonismus. *Biochem. Ztschr.*, 183: 283–297, 1927.
41. Bornstein, A. and Griesbach, W. Ueber Zuckerverbrennung der kuenstlich durchbluteten Leber. Wirkung von Adrenalin und Pilocarpin. *Ztschr. f. d. ges. exper. Med.*, 37: 33, 1923.

Review

Arteriosclerosis*

A Statement of the Problem

RICHARD GUBNER, M.D. *and* HARRY E. UNGERLEIDER, M.D.
New York, New York

"Thus do interpretations throng and clash, and neatly equal the commentators in number. Yet possibly each one of these unriddlings, with no doubt a host of others is conceivable; so that wisdom will dwell upon none of them very seriously."
James Branch Cabell in "Jurgen"

THAT some broad frame of reference is needed in the problem of arteriosclerosis is patent from the widely divergent concepts of its pathogenesis. The many facts which are known about arteriosclerosis have been subject to the most varied interpretations. Thus it is held that arteriosclerosis is a progressive and irreversible affection of the arteries and "one of the indispensable penalties of living,"[1] whereas evidence exists that arteriosclerosis is reversible[2–6] and is not necessarily associated with aging.[7] The lipoid infiltration of the arterial intima and subintima which constitutes the basic pathologic lesion of arteriosclerosis is variously regarded as due to imbibition from the blood stream;[4] as the result of invasion of the subendothelial layer of the artery from the bloodstream by foam cell lipoid-laden macrophages wandering from the liver;[8] as a consequence of extravasation of serum and of hemorrhage from the arterial vasa vasorum;[9,10] as a secondary reactive process to injury of the intima which is, according to this view, the primary lesion of arteriosclerosis;[6] as necrotic débris of degenerated subintimal tissue;[11] and as due to local production of lipid consequent to disorganization of the intima resulting from mechanical strain of the arterial wall.[12]

Divergent opinions are held regarding the permeability of the arterial intima. It is considered on the one hand that decreased permeability of the intima due to coating of the endothelium by a lipoid film, with impaired nutritional supply to the arterial wall, is of prime importance in the genesis of arteriosclerosis,[13–14] and on the other hand that increased permeability of the intima favors the penetration of lipoid.[15,16] The latter view considers that a loosening of the connective tissue ground substance of the intima occurs as part of the colloidal aging process or is due to mechanical strain.

The relation of the serum lipoids to atherosclerosis is also a subject of contention. Atherosclerosis is regarded by some as due to hypercholesterolemia,[17,18] whereas it is stated that there is "no valid reason for believing that a disturbance of cholesterol or lipoid metabolism plays any part in the etiology of human arteriosclerosis,"[6] and it is claimed that hypercholesterolemia is a complication rather than an etiologic factor in arteriosclerosis.[19] Elsewhere it is considered that "atheromatosis is not due to hypercholesterolemia but due rather to a disturbance in the stabilization of the colloid state of cholesterol in the blood,"[13] with factors favoring the precipitation of cholesterol in plasma and tissues. Whereas

* From the Medical Department, Equitable Life Assurance Society of the United States, New York City, and the Department of Medicine, Long Island College of Medicine, Brooklyn, N. Y.

many have considered cholesterol alone as important in the genesis of arteriosclerosis, other serum lipids have been shown to play a significant role as well.[20–23] Factors associated with arteriosclerosis, such as diabetes mellitus (with its frequently attendant hyperlipemia) and hypertension, are considered both causes[24–27] and consequences[1,19,28–31] of arteriosclerosis. The role of the arterial vasa vasorum which has recently attracted much attention has been interpreted both as a prime factor in the genesis of arteriosclerosis[9,10,32] and as a secondary reactive phenomenon.[33,34] Opposite views are held too concerning the primary[8] versus the secondary[6] significance of the "foam" cells which are conspicuous in the histology of atherosclerotic lesions. Apart from differences in opinion as to the significance of foam cells there is no unanimity regarding their origin. Whereas they are considered to be of phagocytic nature,[6,8] it has been suggested that they are endothelial cells which become fat-laden and penetrate into deeper layers of the artery where they disintegrate directly into atheromatous masses.[35]

In the face of such extremes of opinion it is not possible to define with exactitude the relative importance and mechanisms of operation of the various factors which have been demonstrated to bear a relation to arteriosclerosis. Evident it must be, however, that there is no single cause, *sui generis*, of arteriosclerosis. Rather the evolution of the arteriosclerotic lesion appears to be due to multiple factors mutually interrelated in a dynamic mechanism. Although broad gaps exist, the knowledge at present available permits the tentative formulation of a concept of the genesis of arteriosclerosis integrating the various morphologic, physiologic and biochemical aspects.

The artery, no less than other specialized tissues, is an organ with a metabolically active parenchyma (the muscle cells), supporting tissue (fibroblasts and elastic and collagen fibers) and an intercellular medium through which nutrition is brought and waste products are removed. It is the unique arrangement of the circulation through the intercellular medium of the artery which appears in large measure to provide the background for arteriosclerosis. The subject of nutrition of the vascular wall has been admirably reviewed by Ramsey.[36] There appears to be general agreement that the arterial wall is normally nourished from two sources. The adventitia and outer portion of the muscular media are supplied by vasa vasorum from the outer surface of the vessel. The inner layers of the arterial wall, including most of the media, derive their nourishment from the blood flowing within the lumen of the vessel, for the most part by direct diffusion across the intact intimal endothelial membrane. The studies of Petroff,[37] Lange,[38] Anitschkow[16] and Iwanov[39] indicate that normally a constant stream flows through the walls of the large arteries in the direction from lumen to adventitia. Water, salts, dextrose and other blood constituents enter the subintimal tissue spaces in the course of this nutritive process to the vascular wall. Colored substances such as bile pigments and colloidal dyes, e.g., trypan blue, can readily be observed to enter the arterial wall from the blood stream. Lipoids, too, penetrate the intima and are transported externally through the media to be removed by the lymphatics of the adventitia.[40] After passing through the endothelial membrane, the blood transudate, i.e., intercellular fluid, penetrates the entire thickness of the arterial wall and is transported off by the lymphatics and veins of the adventitia.

The same factors which determine the composition and circulation of the intercellular fluid in other tissues of the body operate in controlling fluid movement through the artery. These include the vascular filtration pressure (intravascular pressure minus osmotic pressure of blood), composition of the blood, permeability of the endothelial membrane, physical state of the intercellular medium and barriers to fluid flow, venous and lymphatic removal of the intercellular fluid and adjuvant factors aiding movement and removal of components of the intercellular medium, such as gross

movement of the part and phagocytic activity. The quantitative effects of these several factors differ greatly, however, in relation to their action in determining the intercellular composition and circulation elsewhere in the body.

INTRAVASCULAR FILTRATION PRESSURE

Whereas the filtration pressure in all other tissues of the body is the relatively low capillary blood pressure, in the arteries the arterial blood pressure itself, which is many times the magnitude of the capillary pressure, determines in large part the movement of fluid across the endothelial intimal membrane into the subendothelial tissue spaces. Consequently, no such delicate balance between intravascular filtering pressure and the colloid osmotic pressure of the blood obtains as in the capillaries. The arterial pressure is the dominant factor in determining the penetration of the arterial endothelium by blood constituents. The penetration of substances such as cholesterol may be increased by virtue of this high filtering pressure. It is presumably for this reason that colloids such as cholesterol accumulate to a greater extent in the arterial wall than in other tissues and that the arteries are the most vulnerable organ in the body to degenerative changes.

It is evident a priori, on this basis, that a high level of arterial blood pressure will hasten the deposition of cholesterol and presumably the development of arteriosclerosis. In the presence of hypertension the cholesterol content of the aorta is significantly increased although the serum cholesterol concentration is not elevated.[41,71] The association of atherosclerosis and hypertension is too well known to require comment. Conversely, it is interesting to note that individuals with hypotension are much less apt to develop arteriosclerosis than those with average normal levels of blood pressure. The study of Hunter[42] showed that with a blood pressure twenty points less than average, the life expectancy is decidedly better than that of the average population, the actual mortality in this group being only 71 per cent of the expected, with many fewer deaths from cardiovascular disease. Values in excess of the low optimal level of blood pressure impose an increasing strain on the cardiovascular system, even in the range which has always been regarded as "normal" simply because these are the most common levels. The atherosclerotic changes in the large arteries are in no way qualitatively different in hypertension from the atherosclerosis in the coronary arteries and aorta which develop in the absence of hypertension,[43] but the elevated blood pressure accentuates the development of these lesions.

Arteriosclerosis is not a uniform process throughout the arteries of the body but exhibits definite zones of predilection. The regions predominantly involved are those subject to greatest intravascular pressure. The susceptibility of the coronary arteries to arteriosclerosis is best comprehended as the result of the unusual pressure relationships in these vessels. Arterial blood pressure has two components, static or lateral pressure head and velocity head. When blood flow is obstructed, the velocity head component is transformed into static pressure augmenting the lateral pressure exerted against the arterial wall. This is what occurs in the coronary arteries supplying the left ventricle during systole for there is considerable retardation of systolic flow[44,45] due to the high level of intramural systolic pressure in the left ventricle, particularly in the deeper layers.[46] The resulting high lateral systolic pressure head in the epicardial extramural segments of the coronary arteries may greatly accentuate the development of atherosclerosis, particularly in the vessels supplying the left ventricle. Intramural systolic pressure in the right ventricle and auricles is lower than in the left ventricle and does not cause any considerable retardation of systolic flow.[47] It is for this reason that atherosclerosis is less marked in the right coronary artery and circumflex branch of the left coronary artery which supply these chambers to a somewhat greater extent than does the left anterior

descending coronary artery. As shown by Ehrich, de la Chapelle and Cohn,[48] the left anterior descending coronary artery regularly "ages" much earlier than do the other coronary rami. The vulnerability of the left anterior descending ramus may most reasonably be attributed to the special pressure relationships in this vessel. Particular evidence for this concept is afforded by the data of Horn and Finkelstein[34] which show a striking disparity in the frequency of severe sclerotic changes in the branches of the coronary arteries supplying the left ventricle as compared with a much lower incidence of sclerosis in the branches to the right ventricle. In contrast to the predilection to arteriosclerosis of the main coronary arteries is the almost complete immunity to arteriosclerosis of the immediately contiguous intramyocardial segments of the coronary arteries. This may be attributed in large measure to the high external pressure on the intramural coronary vessels during systole so that the net intraluminary pressure exerted against the vessel wall during systole, at least, is negligibly small or even a minus quantity.

Two other regions of the vascular system exhibit a high incidence of arteriosclerosis and in both the intravascular pressure appears to play a significant role in determining localization. Atherosclerosis is very common in the lower extremities where gravity imposes an increased static (lateral) pressure head. The greater incidence of atherosclerosis in the aorta as contrasted with the smaller peripheral muscular arteries likewise may be attributed to the greater lateral pressure head than velocity head in the large elastic arteries. In the smaller arteries the velocity of blood flow is much greater than in the elastic aortic reservoir and the lateral pressure component is lower. One of the most frequent sites of atherosclerosis of the aorta is in the superior portion of the aortic knob at the junction of the transverse and descending segments of the aortic arch. This is the region most subject to the direct impact of the systolic ejection and the area of the aorta against which greatest intravascular pressure is exerted. The predilection for arteriosclerosis at this site contrasts with the relative freedom from arteriosclerosis in the ascending portion of the aortic arch which is mobile and moves freely with the heart during systolic ejection. Arterial segments which are fixed, as at points of bifurcation and branching in the aorta, or which are immobilized in bony structures and confined tissues, such as the intracranial arteries, are subject to greater pressure impact and are vulnerable to arteriosclerosis. A striking illustration of the importance of restriction of elastic expansion is seen in the greatly increased degree of arteriosclerosis in the posterior wall of the aorta opposite the prominences of the vertebral bodies contrasting with adjacent segments of the aorta which are not fixed and immobile.[1]

Further examples may be cited of the role of intravascular pressure in causing atherosclerosis; among them are arteriosclerosis in the aortic arch proximal to coarctation of the aorta, sclerosis of the mitral valve on the ventricular side, sclerosis of the right ventricular endocardium opposite a patent interventricular septum and of the pulmonary artery opposite patent ductus arteriosus, sclerotic changes in the veins opposite the fistulous opening in arteriovenous fistula, phlebosclerosis wherever veins are subject to prolonged increase in venous pressure, and particularly arteriosclerosis of the pulmonary artery and its branches secondary to pulmonary hypertension caused by such conditions as mitral stenosis and pulmonary diseases leading to cor pulmonale.[1]

PERMEABILITY OF THE ARTERIAL INTIMA

While permeability of the endothelial membrane must be of fundamental importance in determining penetration of lipids to form atheromas, knowledge of this aspect of the problem is still fragmentary. Such information as is available derives from the studies of cellular physiologists on membrane permeability. Even here, as stated by Davson and Danielli,[49] "of the

permeability of natural membranes to fats and proteins very little is known, despite the physiological importance of these compounds." The endothelial membrane consists of the thin endothelial cells and their product, a binding intercellular cement. There is evidence that the membrane is in large measure a thin lipoid layer. The chemical stability of the endothelial membrane, particularly the intercellular cement, controls the permeability of the vessel. The permeability is greatly influenced by many factors. It is increased by lack of oxygen, increased acidity and by many noxious substances such as histamine. It is decreased by thyroid hormone, calcium, ascorbic acid, vitamin P, thiocyanates and caproic acid.[49,50]

So early a student as Virchow believed that heightened permeability is an important determinant in the genesis of arteriosclerosis. His view that a loosening of the connective tissue ground substance of the intima caused by mechanical strain occurred as a preliminary to the imbibition of cholesterol into the subintima is substantially similar to that later expressed by Aschoff[15] who believed that the changes in the intercellular ground substance are to be attributed to colloidal aging. Other investigators, such as Anitschkow,[16] likewise have considered that areas of heightened permeability are important in determining the localization of arteriosclerosis. It was found by Anitschkow that lipoid material is deposited in the subintima in the same regions of the aorta which exhibit greatest permeability to colloidal dyes. Somewhat at variance with this point of view is the theory of Hueper[13,14] that the atheromatous process is initiated by precipitation of a cholesterol film on the intimal surface causing a reduction in permeability of the vessel wall. Hueper believes that the resulting anoxic injury to the endothelial cells secondarily causes increased permeability of the intimal membrane. Increased permeability produced by injury to the intima leads to the formation of subintimal lipoid atheromas.[14,18]

A clinical example of permeability as a factor in arteriosclerosis may exist in the action of the thyroid hormone on vascular permeability. As shown by Lange,[51] deficiency of the thyroid hormone as occurs in hypothyroidism greatly increases capillary permeability and this is reversed by administering thyroid extract. This observation suggests that increased permeability of the intima (in addition to heightened blood cholesterol which is usually present) may be significant in accounting for the well known increased incidence of arteriosclerosis in myxedema. Thyroid deficiency also favors the development of experimental arteriosclerosis.[52,53] Administration of thyroid on the other hand prevents the development of arteriosclerosis.[54,55] This beneficial effect may be due in part to the action of thyroid hormone in decreasing the permeability of the endothelial membrane. Thyroid hormone decreases the amount of lipids, such as cholesterol, in the blood; however, there is some evidence that heightened blood cholesterol may play little or no part in explaining the increased occurrence of arteriosclerosis in thyroid-deficient states.[56,57] However suggestive, the action of thyroid hormone is much too complex to single out its effect on vascular permeability as its sole relation to arteriosclerosis. Iodides and thiocyanates, which also decrease permeability,[49] likewise inhibit the development of arteriosclerosis in animals fed cholesterol.[58–61] Since these substances do not affect the content of cholesterol in the blood or cause resolution of lesions produced by prior administration of cholesterol,[62] their action, like that of thyroid hormone, may be due to their effect on membrane permeability.

BLOOD COMPOSITION: SERUM LIPIDS

The fundamental role of serum lipids in the genesis of arteriosclerosis is emphasized by experimental production of atherosclerosis in the rabbit, guinea pig, chick and dog by sustained dietary elevation of blood cholesterol. Particularly important, because

of its close resemblance to human atherosclerosis in the distribution and character of the lesions, is the production of atherosclerosis in the dog by the feeding of cholesterol combined with thiouracil administration.[53] Clinically it is well known that there is an increased incidence of atherosclerosis in conditions associated with hypercholesterolemia, such as essential xanthomatosis and other lipoidoses, diabetes mellitus, myxedema and nephritis, particularly in the nephrotic stage. It has been reported by some investigators[63,64] that the level of blood cholesterol is significantly elevated in a large percentage of cases with arteriosclerosis although this is still open to question.[65] Of interest as a possible indication of a disturbed cholesterol regulation is the observation that not only are the levels of cholesterol elevated in subjects with coronary arteriosclerosis but the serum cholesterol also fluctuates widely, contrasting with a relative constancy of the serum cholesterol in normal individuals.[64] In a recent study employing the Schoenheimer-Sperry method for blood cholesterol determination, which is more accurate than older methods, it was reported that 68 per cent of seventy-five patients under sixty years of age with coronary occlusion exhibited hypercholesterolemia, with levels of blood cholesterol exceeding 260 mg. per cent.[66] Particularly significant is the demonstration of hypercholesterolemia in young individuals with coronary artery disease, subjects in whom other factors contributing to the development of arteriosclerosis are lacking.[67] Hyperlipemia is also very frequent in younger women with coronary artery disease.[68] The high incidence of arteriosclerosis in groups subsisting on a high fat, high cholesterol diet, as in obese individuals, American soldiers of World War II[69] and inhabitants of the Kirghiz Steppe (who consume enormous quantities of mare's milk[70]) contrasts eloquently with the rarity of arteriosclerosis in groups on a low fat, low cholesterol diet, e.g., orientals and Europeans during the period of semi-starvation following the first World War.[4,71]

Whereas hypercholesterolemia of considerable degree predisposes to the development of atherosclerosis, low levels of serum cholesterol appear to confer some protection. In a study recently carried out by the authors* it was found that the incidence of arteriosclerosis of the aorta was approximately the same in (1) individuals with slight degrees of hypercholesterolemia (22 per cent of eighty-three cases, average cholesterol 300 mg. per cent) as in (2) those with "normal" cholesterol concentration (20 per cent of eighty-four cases, average cholesterol 211 mg. per cent); whereas among subjects with low cholesterol levels (3) significantly less arteriosclerosis was found (7 per cent of seventy-seven cases, average cholesterol 160 mg. per cent). The average ages and body builds in these groups were similar, (1) forty-eight years, 7.8 per cent overweight, (2) forty-six years, 8.3 per cent overweight, (3) forty-seven years, 6 per cent overweight. No relation could be demonstrated between cholesterol level and age or weight. These observations suggest that the so-called" normal" cholesterol is in reality a high cholesterol, and that the cholesterol level of the average American population is of such an order as to predispose to the development of arteriosclerosis.

Although several hypotheses have been invoked to explain the presence of cholesterol in arterial atheromas, the simplest and most reasonable view is that of direct imbibition of lipids from the plasma together with other plasma constituents through the intimal endothelium under the influence of the high filtering arterial pressure. Chemical analyses indicating that atheromas are not constituted of cholesterol alone but contain the same lipids as are present in plasma[20–23] support this concept. Not only lipids but other macromolecular substances in the colloidal state penetrate through the vascular endothelium into the arterial subintima,

*Ungerleider, H. E., Gubner, R. and Rodstein, M. Clinical significance of blood cholesterol. Presented at the Annual Meeting of the American Society for the Study of Arteriosclerosis, Chicago, Oct. 31, 1948.

such as amyloid[72,73] and hyaline[74] which derive in part from the serum proteins. Exogenous agents such as the colloidal dyes Evans blue,[75] fluorescein and naphthol yellow,[76] trypan blue and lithium carmine[77,78] similarly penetrate the vascular endothelium to enter the vessel wall. Atheromatous lesions closely resembling experimental cholesterol atheromatosis and human atherosclerosis have been produced by administration of a variety of macromolecular colloidal carbohydrates,[13] such as polyvinyl alcohol, methyl cellulose, pectin and acacia which enter the arterial subintima by penetration through the endothelium.

Accepting the hypothesis that cholesterol enters the arterial subintima by direct penetration through the endothelium, the mechanism of this transport still remains to be answered. There are at least two ways in which such penetration might occur. Serum cholesterol exists in large molecular colloidal aggregates or micellae[79,80] in close association with the serum proteins, particularly the globulin fractions.[81,82] Serum cholesterol may be precipitated with protein, at least with ammonium sulfate fractionation, and passes graded ultrafilters only in association with and in proportion to protein.[83] Evidence exists also that cholesterol and protein pass through natural membranes in close association. The concentration of lipids in transudates bears a direct relation to the concentration of lipids in the serum.[84] The concentration of lipids in the urine parallels the urinary excretion of protein in conditions of increased glomerular permeability producing proteinuria,[85–87] and the same relationship occurs in the spinal fluid in disorders associated with increased spinal fluid protein content.[88] In view of this close association it seems possible that cholesterol, as well as other serum lipids, enters the vessel wall by penetration together with protein under the influence of the arterial filtering pressure. Tissue utilization of hydrophilic colloids such as protein and lecithin, which hold the hydrophobic cholesterol in colloidal dispersion,[21,89] might lead to precipitation of cholesterol in the arterial wall.

An alternative possibility is that cholesterol precipitation occurs first in the bloodstream before penetration into the vessel wall. Although the tissues of most mammals contain approximately the same amount of cholesterol as the corresponding tissues of man, human blood plasma has a higher cholesterol content than any other species[90] and normally stands at a level not far from the point of saturation.[91] The solubility of cholesterol in the serum, as determined by Loeper's test,[92] varies greatly, with a striking decrease in older individuals beyond the sixth decade, particularly, it is claimed, in subjects with arteriosclerosis.[81,93] Eck and Desbordes[93] attribute the finding of normal cholesterol levels in the majority of subjects with arteriosclerosis to inability of the serum to dissolve more cholesterol with resulting precipitation in the blood stream along the vascular channels. These investigators, as well as others such as Alvarez and Neuschlosz[94] and more recently Hueper,[13,14] hold the view that the colloidal stability of cholesterol in blood plasma rather than its concentration is the significant factor in the genesis of arteriosclerosis. Hueper believes that the atheromatous process is initiated by an imbalance of the plasma colloidal equilibrium which he attributes to vibration of the blood column, causing the precipitation on the intima of a cholesterol film which penetrates the endothelium. It is difficult to reconcile this concept with the clinical observation that arteriosclerosis is increased in the nephrotic state, in which condition a greatly increased amount of cholesterol is "dissolved" in the serum as a cholesterol globulin colloid complex.[95]

In the light of present knowledge, regulation of the blood cholesterol appears to offer the most promising approach to the prevention of arteriosclerosis. Analysis of the mechanisms whereby blood cholesterol may be lowered requires a brief resumé of the factors controlling cholesterol metabolism. Although cholesterol plays a determin-

ing role in the genesis of arteriosclerosis it cannot be regarded entirely as a noxious agent. Cholesterol serves important physiologic functions as a constituent of all body tissues, as a precursor of cholic acid and steroid hormones and as a vehicle for fatty acid transfer. Cholesterol metabolism, particularly in relation to its concentration in the serum, is best viewed as an adjunct to fat transport.

Cholesterol in the body derives from two sources, synthesis in the liver and ingested cholesterol in the diet. Synthesis of cholesterol in the body is restricted to the liver, the precursors being simple chemical units such as acetic acid as shown by deuterium tag studies.[96] Acetic acid derives from fatty acids by the mechanism of β-oxidation with removal of acetyl groups from the β-keto acids. Acetic acid contributes to the formation of the entire steroid molecule, with fully half of the hydrogen atoms and probably half of the carbon atoms furnished by acetate.[97] Apart from synthesis of cholesterol, the liver regulates steroid metabolism in many ways including the formation of cholic acid from cholesterol,[98] degradation of steroid hormones and the transfer of fatty acids esterified with cholesterol to phosphatides, with excretion of free cholesterol as well as of bile acids in the intestines via the biliary tract. The daily biliary excretion of cholesterol is at least 0.5 Gm. and of bile acids 2 Gm. The cholesterol in the bile as well as that in the diet is in the free (non-esterified) form.[100] The daily cholesterol intake in the mixed diet of the adult varies from 200 to 360 mg.; on a low-fat diet it ranges from 39 to 109 mg.; whereas fat-rich diets may contain up to 1,400 mg. of cholesterol.[90]

In the intestines cholesterol serves as a major vehicle for the absorption of fatty acids, particularly the highly important unsaturated fatty acids. The mechanism whereby this occurs may be briefly described as follows: fatty acids which are liberated by the action of pancreatic lipase on neutral fat are then esterified with cholesterol by pancreatic cholesterol esterase, which is activated markedly by bile acids[101,102] in particular by cholic acid and glycocholic acid.[103] The esterified cholesterol is transported into the epithelial cells of the intestine, unesterified cholesterol itself being absorbed poorly if at all. To be absorbed, therefore, cholesterol requires the presence of fat, pancreatic enzymes and bile salts. If any of these be lacking, cholesterol absorption is greatly impaired. Thus, in animals on a fat-free diet cholesterol which is administered can be recovered quantitatively in the feces.[104]

Fatty acids are absorbed not only as cholesterol esters but by other mechanisms as well. Some neutral fat emulsified by bile is absorbed directly, passing into the lymphatics, but the major portion of fat is hydrolyzed by lipases into glycerol and fatty acids. The shorter chain, water-soluble fatty acids as well as glycerol pass directly into the blood stream. The remaining fatty acids, particularly the unsaturated fatty acids, are assimilated both as cholesterol esters in the manner already indicated and by phosphorylation in the intestinal mucosa to form phosphatides, lecithin being the principal vehicle for fatty acid absorption. Phosphorylation by the intestinal mucosa is an important mechanism for the absorption of fatty acids, as indicated by the finding of radioactive phosphate given orally with fats[105] or intravenously[106] in the phosphatides of the intestinal mucosa. Further indication of the importance of phosphorylation in fatty acid absorption may be afforded by the observation that fat absorption is markedly impaired by iodoacetate and phlorizin which inhibit phosphorylation[107] although this has been denied. The fatty acids of the blood phospholipids represent in large part the fatty acids of newly absorbed fat, i.e., fatty acids in transport.[108]

These various mechanisms of fat absorption are mentioned because both in absorption and in transport in the blood stream (as indicated by blood concentration) there appears to be a remarkably constant concentration and division of the various lipid

fractions in any individual, suggesting a dynamic interdependence and relationship. Particularly is this true for the ratios cholesterol/cholesterol esters and cholesterol/phospholipids. Neutral fat which usually comprises the smallest fraction of the fatty acids of the plasma is somewhat more independent and variable.[109] The clinical significance of the close interrelation between the various lipid fractions of plasma lies in the realization that blood cholesterol concentrations must not be considered alone but in terms of lipid metabolism as a whole. The reason for the constancy of the partition of fatty acids between cholesterol esters and phospholipids lies in the regulatory activity of the liver in transferring fatty acids from cholesterol to phosphatides, as will presently be mentioned. Bloor[102] has suggested that the constant relationship between cholesterol and phospholipid is useful to the organism in preserving colloidal equilibrium since phospholipid is hydrophilic and cholesterol is hydrophobic.

The hydrophobic, insoluble cholesterol owes its high concentration in the serum of man to agents which allow it to be carried in colloidal dispersion. Phospholipids, as Bloor has suggested, may be significant in this regard. Even more important is the vehicular role of the blood proteins which combine with the blood lipids to form lipoprotein complexes. Electrophoretic studies have indicated that serum lipids are in large part bound to serum proteins, chiefly in a relatively weak bond. Both cholesterol and phospholipids are present in highest concentration in the $alpha_2$ and beta globulin fraction.[81,82] Appreciable quantities are also attached to serum albumin and gamma globulin. Lower fatty acids on the other hand exhibit a high electrostatic affinity for serum albumin as shown by electrophoretic studies.[110] The marked increase in serum cholesterol which occurs in the nephrotic state[95,111] may in part be due to the large increase in $alpha_2$ and beta globulin in this condition, the increased globulin holding more cholesterol and phospholipid. To some extent the unusually high alpha and beta globulin peaks in the electrophoretic spectrum in nephrosis, seen also to a lesser degree in hypothyroidism,[112] must be attributed to elevated cholesterol itself for on extraction of the plasma with ether, removing lipids thereby from their protein complexes, these large peaks become considerably reduced. The globulin-lipid bond is ruptured by heparin with liberation of the combined lipids and the simultaneous formation of a protein-heparin compound.[113] Since heparin has been reported to cause rapid disappearance of alimentary lipemia in dogs,[114] it would be of great interest to determine the effect of heparin on blood cholesterol and phospholipids in clinical hyperlipemia states as a possible means of lowering elevated blood cholesterol.

While the serum proteins by virtue of their binding capacity appear to exercise some influence on the level of the serum lipids, a more dynamic role is played by the liver. In the liver, cholesterol esters, which are formed in the intestine as a vehicle for fatty acid absorption and transport, are transferred to choline phosphatides, i.e., lecithin, in preparation for further stages of fat metabolism. The turnover rate of liver phospholipids is accelerated by choline and its precursors[115] whereas the transfer of fatty acids from cholesterol esters is impaired in choline deficiency and in hypothyroidism.[102] The mechanism of action of choline and thyroid hormone are interrelated for choline must be present for thyroxine to exert lipotropic action.[116] In fatty livers produced by choline deficiency a great accumulation of cholesterol esters occurs in the liver. Conversely, lipotropic agents such as lecithin, choline, methionine, inositol, betaine and thyroid hormone speed up the removal of fatty acids from cholesterol, allowing the liver to pass free cholesterol into the bile.

It is evident from these remarks that serum cholesterol, functioning as a vehicle for fatty acids, can be elevated by any mechanism which elevates the blood fat. Known mechanisms include: (1) impaired

removal of fatty acids by the liver, e.g., in myxedema and in choline deficiency; (2) increased fat in the diet which causes increased reabsorption of cholesterol spilled into the intestine in the bile; (3) mobilization of fat from fat stores as occurs in starvation[117] and when utilization of carbohydrate is impaired, as in severe diabetes and during phlorizin administration.[109] (4) An increased capacity of blood to bind lipids associated with elevated globulin concentration may be partially responsible for hypercholesterolemia such as occurs in the nephrotic state, although other factors doubtless play a part. (5) Increased synthesis of cholesterol by the liver is another mechanism which probably is important in the production of hypercholesterolemia, e.g., in diabetes mellitus in which increased fat utilization may provide a greater acetate pool for synthesis into cholesterol.

Attempts to lower blood cholesterol have been directed principally toward the speeding up of hepatic removal of lipids with lipotropic agents, i.e., augmented transfer of fatty acids from cholesterol esters to phosphatides. Experimentally, lecithin and choline fed to rabbits receiving cholesterol restrict hypercholesterolemia and diminish the incidence of arteriosclerosis in these animals.[118] While some success has been claimed with the use of these and other lipotropic agents in lowering elevated blood cholesterol in man,[119,120] their clinical value is at best limited; for such decreases in serum cholesterol as are accomplished are transitory and are not maintained beyond five weeks despite continued administration of lecithin.[121] It is understandable why lipotropic agents in themselves are relatively ineffective in lowering blood cholesterol. These agents accomplish the removal of fatty acid esters from cholesterol in the liver, allowing free cholesterol to be excreted in the bile. However, the biliary cholesterol is promptly reabsorbed in the intestines, back into the circulation, unless cholesterol absorption is prevented by extreme fat restriction or other measures to be considered.

Actually the bile is not an important medium for excretion of cholesterol.[102] Biliary cholesterol is one phase in the physiologic circulation of cholesterol (intestine → blood → liver → bile → intestines) in its role as an adjunct in fat transport rather than a major excretory pathway of cholesterol. If bile is excluded from the intestines by a biliary fistula or by closure of the bile duct,[122] large amounts of sterols are still found in the feces, unaccounted for by the dietary intake. The major part of sterol excretion takes place directly into the intestine, particularly the large bowel.[102] Just how this occurs has not been explained but the following mechanism may be advanced as plausible. Cholesterol is not stored in the body as is fat, fatty tissues containing no cholesterol or only minimal amounts.[123] However, a considerable repository of cholesterol is present in the leukocytes.[124,125] With the development of infection, both in animals[126] and in man,[127] blood cholesterol falls, the serum cholesterol and lipid content tending to vary inversely with the total leukocyte count in infection.[102] Lymphocytes pass into the intestine in enormous quantities, this being their main pathway of diposal by the body.[128] Generated (as the greater number of lymphocytes are) in the lipid-rich environment of the mesenteric lymphatics and excreted after circulation in the blood into the intestines, lymphocytes may well provide an important mechanism for excretion of sterols. A considerable amount of cholesterol excreted in such manner may be reabsorbed just as biliary cholesterol. It is apparent that an important phase of cholesterol metabolism is exogenous in the intestinal tract. Attempts to deplete the body of cholesterol by an attack on this exogenous phase of cholesterol metabolism appear, as will be outlined, to offer perhaps greater promise than endogenous methods operating within the body tissues.

Destruction of cholesterol in the body has not yet been shown to occur in any appreciable degree and may be of little physiologic consequence in regulating blood

cholesterol. Cholestanol, the hydrogenation product of cholesterol, is found in small concentration in the blood serum,[129] and cholestenone, the unsaturated ketone which is the initial stage in degradation to coprosterol, has been isolated in body tissues.[130] One further endogenous aspect of cholesterol metabolism is of some consequence, however, in determining the level of serum cholesterol. Cholesterol is synthesized in the liver. In view of the constant level of serum cholesterol it is probable that a daily synthesis of approximately 0.3 Gm. occurs in man to offset the average negative balance of this amount.[102] It is quite possible that increased hepatic synthesis of cholesterol may be responsible for hypercholesterolemia in cases in which other factors which are known to elevate blood cholesterol do not appear to play a part, i.e., essential familial hypercholesterolemia. The effect of fat in elevating blood cholesterol may be due not only to promotion of intestinal absorption of cholesterol, but perhaps in even more important measure to supplying large quantities of acetate, a building block of cholesterol. The relative significance of exogenous and endogenous cholesterol in contributing to hypercholesterolemia and atherosclerosis awaits clarification by studies with the isotope technic. Clinical evidence that hepatic synthesis of cholesterol and cholesterol esters has an important bearing on the level of blood cholesterol is afforded by the fact that severe liver disease leads to a decided fall in blood cholesterol, particularly of the esters. It remains to be determined whether hepatic synthesis of cholesterol can be decreased, however, without seriously disturbing other important hepatic physiologic functions. Acetic acid metabolism, which is of fundamental importance in cholesterol synthesis, is profoundly affected by sodium fluoroacetate which, because of its close similarity to acetate, blocks enzyme systems concerned with the utilization of acetate by competitive inhibition.[131] The toxicity of this compound may preclude clinical application for such purposes as decreasing cholesterol synthesis. Other substances less disturbing to the body economy interfere with cholesterol metabolism, and it may be that an effective agent of sufficiently low toxicity can be employed to decrease cholesterol synthesis. Sulfite, a reagent which blocks aldehyde groups, inhibits sterol synthesis from acetate in yeast but does not impair fat synthesis. Cinchophen in doses which do not ordinarily seriously impair hepatic function causes marked suppression of cholic acid synthesis and excretion;[132] and cholic acid, it is recalled, derives from cholesterol. Thiocyanate is stated to decrease blood cholesterol, presumably due to its effect on the liver[133,134] although elsewhere this action is questioned.[135,136] Sympathomimetic drugs and calcium salts cause hypocholesterolemia[137] and in this connection it is of interest that epinephrine increases fecal lipid excretion.[138] An interesting reciprocal relation exists between the level of blood cholesterol and urea. Blood cholesterol is decreased in uremia,[139] and elevation in the blood urea following the ingestion of urea by human subjects is often accompanied by a striking fall in the plasma cholesterol.[140] A direct relationship is stated to exist between the cholesterol content of the tissues and blood and the degree of hydration, i. e., salt content of the body.[141,142]

Such observations leave no doubt that endogenous mechanisms may influence the level of serum cholesterol but no effective means has yet been found to lower serum cholesterol for sustained periods based on mechanisms operating in the body tissues proper. However, the lowering of blood cholesterol by dietary restriction of fat may, as has already been suggested, be due in large measure to decreased hepatic synthesis of cholesterol consequent to a restriction of the acetate precursor of cholesterol. As has been indicated, cholesterol in its metabolic cycle passes through an external phase in the intestines. This appears to be the most vulnerable site for depleting the body of cholesterol. The mechanisms of attack on the exogenous phase of cholesterol metabolism may be outlined as follows:

A. Decrease Ingested Cholesterol. Dietary restriction of cholesterol, although undoubtedly an adjuvant of some utility in any regimen attempting to lower blood cholesterol, has not been found effective of itself. Little or no effect on the blood cholesterol has been observed in prolonged dietary studies employing very low or very high cholesterol diets.[143,144]

B. Decrease Absorption of Cholesterol. 1. *By reducing the fat content of the diet:* Fat is important not only in cholesterol synthesis but in cholesterol absorption as well. Hypercholesterolemia occurs after administering fat alone,[90] the blood cholesterol rising during absorption of fat parallel to the increase in blood fatty acids.[102] As Bloor[102] has pointed out, the part played by the bile in supplying cholesterol to the blood has generally been overlooked, and the cholesterol of the bile, reabsorbed during fat absorption, may be sufficient to explain the increase in blood cholesterol after feeding of fat. Absorption of cholesterol occurs only in the presence of fatty acids. On a fat-free diet the cholesterol given can be recovered quantitatively in the feces.[145] A quantitative relationship has been found between the cholesterol content of the bodies of rats and the amount of fat fed on a constant sterol-poor diet.[146] Likewise the absorption of bile acids is decreased on a low-fat diet.[147] Clinically it has been shown that high-fat diets in diabetics favor and low-fat diets retard the appearance of hypercholesterolemia and arteriosclerosis.[26] Significant decreases in blood cholesterol have been observed with the Kempner rice diet which has a very low fat content of approximately 5 Gm.[148] Unless dietary restriction of fat is extreme little or no effect on blood cholesterol can be anticipated.

2. *By exclusion of bile from the intestines:* In view of the fact that considerable cholesterol depletion is effected by a biliary fistula,[149–152] protracted non-surgical biliary drainage might accomplish considerable loss of cholesterol and bile acids. As already observed, the daily biliary excretion of cholesterol is at least 0.5 Gm. and of bile acids 2 Gm. Increased biliary excretion of cholesterol and temporary lowering of blood cholesterol result from administration of lipotropic agents,[119–121] and (it is said) the feeding of powdered leaves of artichokes[153] and eggplant[154] or injection of their aqueous extracts. Such agents would undoubtedly be more effective in decholesterinization if intestinal reabsorption of the cholesterol excreted via the bile could be prevented.

3. *By interfering with pancreatic enzymes which are necessary for the esterification of cholesterol with fatty acids:* It is of interest to note that in steatorrhea due to pancreatic insufficiency the blood cholesterol is unusually low.[155] Absorption of fat is impaired by quinine[156] and by sodium cetyl sulfate[157] which inhibit lipases, thereby preventing lipolysis of neutral fat into fatty acids. Phosphorylation of fatty acids is an important mechanism for their absorption. As already indicated fat absorption may be markedly impaired by iodoacetate and phlorizin which inhibit phosphorylation.[107] Intestinal phosphate can be tied up and made unavailable for phosphorylation by administering aluminum hydroxide gels, which, in daily dosage of 120 to 160 cc., reduce urinary phosphate excretion by 90 per cent.

4. *By esterifying cholesterol with non-absorbable fatty acids:* Long chain fatty acids are poorly absorbed; arachidic acid of peanut oil, for example, is almost wholly excreted in the feces.[158]

5. *By physical means which prevent cholesterol absorption:* It has been shown that 20 cc. of liquid petrolatum taken two or three times daily before meals interferes with the absorption of carotene.[159] It appears possible that the absorption of cholesterol might similarly be decreased and fecal excretion augmented by non-absorbable fat solvents such as mineral oil, or by steroid adsorbing agents such as silica gel.

C. Increase Degradation of Cholesterol in the Intestines. 1. Bacterial destruction of steroids in the intestine. This is an important physiologic mechanism for the excretion of cholesterol. Cholesterol which is not esteri-

fied with fatty acids in the intestine to be absorbed is in part excreted unchanged in the feces, the greater amount, however, first being degraded in the colon before excretion. Degradation of cholesterol, which occurs in the body tissues to a negligible degree if at all, is accomplished by putrefactive bacteria in the colon.[160] One must conclude that these bacteria exercise an important physiologic function in augmenting the excretion of cholesterol by degrading it into non-absorbable steroids, principally coprosterol. Different strains of coliform organisms vary greatly in their ability to destroy steroids.[161] When the bacterial flora of the colon is decreased by administering succinyl-sulfathiazole, the formation of coprosterol is abruptly halted.[162]

The degradation of cholesterol proceeds by oxidation to the ketone cholestenone followed by reduction to coprostanone and further reduction to coprosterol.[163] The primary oxidation of steroids to the keto form appears to occur in the cecum through the action of the micro-organisms Alkaligenes faecalis and Escherichia coli, as shown by studies of cholic acid catabolism.[164–168] The sequence of chemical changes in cholesterol degradation may be represented in the following manner: cholesterol ⇄ cholestenone → coprostanone → coprosterol. Coprostanone and coprosterol cannot be absorbed from the intestine and once formed are excreted. Cholestenone, however, can be reconverted to cholesterol. The pathway taken by cholestenone depends on factors in the gastrointestinal tract and on the diet. In dogs fed cholestenone with a biscuit diet most is converted to cholesterol, whereas on a meat diet most of the cholestenone administered is excreted as coprosterol.[169] It is probable that the effect of diet on coprosterol formation is due to the determining influence of diet on the intestinal flora, a high-protein meat diet greatly favoring the predominance of coliform organisms[170–172] which possess the ability to degrade cholesterol. A certain portion of cholesterol is degraded by reduction to dihydrocholesterol which, like coprosterol, is not absorbed and is excreted in the feces. It appears, therefore, that a high protein diet may afford a means of augmenting the conversion of cholestenone to coprosterol, decreasing the amount of cholestenone available for reconversion to cholesterol. It would appear worth while to explore the possibility of implanting strains of coliform organisms which possess a high capacity to accomplish degradation of cholesterol, since, as already mentioned, there is a marked difference in the ability of various strains of coliform organisms to alter steroids.

2. *Chemical destruction of steroids in the intestine:* The observation that cooked brain administered in the diet, both to rats[173] and dogs,[174] augments the formation of cholestenone from dietary cholesterol and causes a striking increase in the fecal excretion of coprosterol to fully 80 per cent of the fecal sterols is of great interest. It is believed that the substance which enables the organism to convert such large amounts of cholesterol added to the diet into coprosterol via cholestenone is identical with or allied to the cerebroside phrenosin.[173] The possibility of augmenting cholesterol depletion in man by this means certainly merits investigation.

Numerous other chemical methods are known which, *in vitro* at least, degrade cholesterol and cholestenone. Thus cholestenone may be formed from cholesterol by the action of selenium dioxide[175] and other oxidizing agents,[176] e.g., cupric oxide.[177] Cholestenone may be fixed by ketone reagents as described by Girard,[176] in particular by the hydrochloride of the hydrazide of betaine. Dinitrophenylhydrazine likewise combines with the unsaturated ketone cholestenone.[175] The aldehyde blocking reagent sulfite has been shown to inhibit sterol synthesis from acetate in yeast.[97] Cholestenone is reduced chemically by many agents such as aluminum isopropylate.[178] To what degree such chemical agents can be employed *in vivo* remains to be determined.

The reduction of cholesterol, to form dihydrocholesterol which, like coprosterol, cannot be absorbed from the intestines, is

slow and appears to offer less promise than the other methods considered.

It is not possible to predict, a priori, which of the several agents considered will be found most feasible or effective in reducing blood cholesterol. It is apparent, however, from the above considerations of cholesterol metabolism that both in endogenous and exogenous phases cholesterol and fat are linked intimately. If cholesterol is the actual culprit in arteriosclerosis, fat is an active accomplice. Not only are cholesterol and fat found together in food sources, but they are integrally associated in intestinal absorption, in transport in the blood stream and in early atheromatous deposits. Perhaps the most important connection is the supplying of acetate by fatty acid breakdown as the major precursor in cholesterol synthesis. Stringent restriction of dietary fat, therefore, appears implicitly indicated in any regimen for lowering blood cholesterol. Experience indicates that slight to moderate dietary restriction of fat is of little value in this regard. If, as appears probable, the cholesterol level of the average American population is at such a high level as to predispose to arteriosclerosis, such a regimen of marked fat restriction should apply not only to individuals with hypercholesterolemia but to the general population as well. This would imply a drastic change in the American diet with far reaching effects on the nation's economy. Before any such program can be urged as a public health measure alternative methods for lowering blood cholesterol should be sought; and it must be more firmly established (1) that low levels of cholesterol indeed protect against arteriosclerosis and (2) whether it is practicable to lower and maintain a low cholesterol level through diet alone.

REMOVAL OF LIPOIDS FROM THE ARTERIAL WALL

The intercellular fluid circulation, which brings nutrients and other constituents of the blood plasma into the vessel wall, is also responsible for their removal. The circulation through the vessel wall can be observed by following the flow of India ink from the bloodstream across the intact endothelial membrane, through the intercellular spaces of the subintima and media to enter the lymphatics of the adventitia and ultimately the regional lymph nodes.[39] Lipoid substances, too, follow this path of circulation and are transported through the arterial wall to be absorbed by the lymphatics.[179] Interference with lymphatic and vasa vasorum drainage of the intercellular fluid causes an accumulation of colloids, such as lipoids, in the arterial wall and impaired nutrition to the cellular elements of the artery, favoring the development of atherosclerotic and degenerative changes. This has been produced experimentally by injuring the adventitia by cautery[180] and is observed clinically in luetic aortitis. Injury to the arterial adventitia causes edema and hemorrhage in the intima; and if combined with cholesterol and thiouracil feeding in dogs, subintimal aortic atheromas are produced in regions underlying the injured adventitia.[181] The atherosclerotic changes in the inner and medial layers of the aorta in regions underlying the areas of luetic involvement of the adventitia in all probability result similarly from interference with the circulation of tissue fluid through the aortic wall.

Certain factors aid the removal of such colloids as cholesterol from the subintimal tissue spaces of the arteries where they are prone to aggregate. Movement and massage in the arterial wall, just as in other tissues of the body, assist the flow and removal of such substances. As suggested by Wilens[182] on the basis of experimental observations, the areas where lipoids accumulate permanently to form atheromas are not necessarily the same points at which they penetrate the intimal endothelial membrane from the blood stream, but rather they represent areas in which the lipoids aggregate by a process of intramural migration through the subendothelial tissue spaces of the arterial wall. The relative freedom from arteriosclerosis of muscular arteries, such as those of the diaphragm[183] and in the popliteal space,[184] is probably due to movement and

massage of these vessels causing lipoid migration. Arterial segments which are immobilized in bony structures or confined tissues such as the intracranial arteries, or are fixed as at points of bifurcation and branching, are particularly prone to arteriosclerosis. Of interest are the observations of Westenhöffer[185] and Moschkowitz[1] that atherosclerotic involvement of the posterior wall of the aorta occurs earliest and is most marked opposite the prominences formed by the projecting upper and lower borders of the vertebral bodies while the regions of the aorta opposite the middle portions of the vertebrae are comparatively free of arteriosclerosis. The factor of heightened pressure during systolic impact on unyielding vascular segments undoubtedly is important as well as impairment of intramural lipoid migration. A further illustration of the importance of movement and massage in preventing aggregation of lipoids is seen in the branches of the coronary arteries in the myocardium which are subjected to the constant movements and massage caused by contraction of the heart. Arteriosclerosis is infrequent in these intramural branches of the coronary arteries,[34] whereas the immediately contiguous main coronary arteries which lie outside the heart muscle are among the vessels most vulnerable to arteriosclerosis.

Another mechanism operates to aid in removing from the subintima lipoids which constantly enter from the bloodstream. This is phagocytosis by endothelial cells and histiocytes. Just as the other factors which contribute to the deposition and removal of colloids from the intercellular tissue fluid medium of the artery are illustrative of physiologic processes which operate in tissue fluids throughout the body, so, too, is phagocytosis of large colloidal molecules, which cannot circulate freely through tissue fluid to be removed directly via the lymphatics, a function which is not unique in the arterial wall. It does not appear reasonable to attribute any special significance to the lipoid-laden macrophages, the foam cells, which are regarded by Leary[33] as wandering from the liver and playing a primary role in the deposition of lipoid in the formation of atheromas. That the occurrence of foam cells is in fact a secondary phenomenon is indicated by the studies of Duff[6] who observed that anisotropic lipoid appears extracellularly in the intima before any fat-containing cells are to be found. The observations of Hueper[14] in experimental atherosclerosis caused by a variety of macromolecular colloidal carbohydrates also indicate the secondary phagocytic nature of foam cells; the colloidal carbohydrates penetrating from the blood stream into endothelial cells and also directly into the subendothelial space where they are taken up by phagocytes which are thereby transformed into foam cells. Such foam cells migrate through the wall of the artery in the intercellular ground substance and spread out between the muscle cells in the media. They aggregate in the adventitial layer around the vasa vasorum whence they are removed.

In addition to mechanical influences and phagocytosis, chemical factors probably play an important role in the disposition of colloids which enter the arterial wall. Of particular interest is the observation that the distribution of lipids in the arterial wall and in early atheromas is very similar to that in the blood,[20–23] whereas in a more advanced stage of atheromatosis there is a greatly increased proportion of cholesterol and a decrease in the ratio of neutral fat and fatty acids.[21,23,186,187] Neutral fats and fatty acids are much more readily removed from the intercellular medium of the vessel wall than is cholesterol,[188] probably being utilized in part by the tissue cells of the vascular wall. It has been suggested by Leary[2] that fibroblasts in the vascular wall bring about cholesterol lysis in atheroma. The fibroblasts, containing an excess of fatty acids, take up cholesterol and in these cells cholesterol esters are split, anisotropism is lost and the cholesterol is brought into solution in an excess of fatty acids; solution of cholesterol being followed by its disappearance from the lesions. Lipoid

changes effected in fibroblasts of the aorta are influenced by an agent in the blood plasma for which the name "antilipfanogen" has been proposed.[189] This heat-labile factor opposes the formation of fat granules in tissue cultures of aortic fibroblasts, presumably by promoting cellular utilization of fatty acids. It is reported that this factor, which is contained in Cohn's albumin "Fraction V," is decidedly low in subjects with coronary artery disease in ratio to the fat depositing lipoid materials of the serum (lipfanogens).[189] If cholesterol lysis by fibroblasts is an important factor in the disposal of cholesterol in the vascular wall as emphasized by Leary, an explanation may be offered for the predilection of atherosclerosis in regions where the intimal cushion is thickest, an anatomic circumstance recently pointed out by Dock[190] to account for the frequency of atheroma in males and in the coronary arteries in particular. Where little intercellular tissue space is present in the subendothelial layer, lipoidal material aggregates in the endothelial cells and histiocytes,[191] whereas in a thick intima with abundant intercellular space a greater amount of lipoid exists free in the tissue spaces outside the cells where it undergoes precipitation.

Agencies thus exist to effect the removal of colloids from the arterial wall although these are not particularly effective for cholesterol. Arteriosclerosis in its early atheromatous stage is not an irreversible process.[2–6] Small atheromatous accumulations of lipoid are regularly observed in the subintimal layer of the aorta in infants which disappear with further growth.[4] If ingestion of cholesterol is discontinued in animals in whom atheromatous changes have been produced, the lesions slowly regress and the lipoid atheroma are gradually resorbed.[6] However, the mechanisms for the removal of lipoid from the arterial wall are not adequate to dispose of the lipoids constantly penetrating through the endothelial membrane. Over the span of decades increasing accumulation of lipoids occurs,[21,71,186,187] particularly in regions where the subintimal tissue spaces are most abundant,[190] with the development of arteriosclerosis in progressively increasing degree with advancing age. Such increase in concentration of lipoids leads to their precipitation, for the concentration of cholesterol in the blood stream in man is at a level not far from the point of saturation.[91]

AGING AND ARTERIOSCLEROSIS

There is a broad basic pattern of change in the intercellular environment common to all aging tissues. This has been studied in greatest detail in the arteries but as pointed out by Burger and Schlomka,[192] and by Aschoff,[15] changes similar to or identical with those in the arteries attend the process of aging in other body tissues such as the crystalline lens of the eye, cartilage, bones, tendons and muscles, the heart and its valves, veins and the supporting framework of the spleen and kidney. Basically these changes consist of an accumulation and alteration in the colloidal constituents of the intercellular fluid. The accentuation of such age changes in the artery is to be attributed to the uniqueness of the factors determining its intercellular fluid formation and circulation, i.e., the high vascular filtration pressure which greatly increases the filtration of colloids from the blood stream across the endothelial membrane. The cholesterol content of the normal aorta increases with age, the increment being accentuated in individuals with hypertension, i.e., heightened vascular filtration pressure.[41]

The increasing accumulation with age of protein and lipoidal substances in the intercellular medium of various tissues was known to Virchow and has been studied in specialized aspects by many investigators. A progressive increase in the deposition of collagen in the intercellular tissue medium occurs with advancing age.[193,194] There is an accumulation of other protein-polysaccharide complexes, too, such as hyalin and mucin.[195] Equally significant is the progressive increase with age in the amount of lipoids such as cholesterol, fatty acids,

lecithin and neutral fat, which accumulate in the intercellular fluids by passage from the blood stream across the capillary endothelial membrane.[71,184,196,197]

Not only do the intercellular colloids accumulate with age but they undergo important physical changes. Thus Bensley[198] has shown that the intercellular ground substance varies markedly with physiologic age. Originally a continuous jelly-like homogeneous substance derived from connective tissue fibroblasts, there occurs with increasing age a progressive condensation with the formation of reticular fibers which develop to form collagen and elastin. The colloidal changes with age, as Wells[91] has emphasized, are similar to the changes which occur in all colloidal gels such as rubber or gelatin with aging. Cited by Wells[91] and others[199–201] as the basis of aging of protoplasm, such colloidal changes more properly apply to the intercellular fluid than to cellular protoplasm. The cellular protoplasm, just as the intercellular fluid, is in a colloidal state. The cell, however, by extracting energy from the environment is able to preserve its "orderliness," or a low state of entropy, to use Schrödinger's phrase,[202] and so to maintain its normal colloidal properties. With a suitable environment, as tissue culture studies have made clear, the cell is potentially immortal. The intercellular fluid on the other hand, although part and parcel of the body, is not truly a living unit and is not possessed of the vital properties necessary to maintain its functional equilibrium. The inanimate intercellular colloidal fluid is subject to the same physical deterioration with age as affects all non-living colloids. Obeying the law of all matter, with progressive increase in entropy the properties of colloids are altered and they lose their ability to bind fluids, with consequent changes in their physical characteristics. Due to loss of similar electric charges, whose repellant effect keeps colloidal particles in a finely dispersed state, their fine dispersion is diminished with aggregation into coarser granular phases, their adsorptive capacity is decreased with a reduced ability to bind water and there is a decrease in their elasticity, permeability and chemical reactivity.[91] Ultimately the colloidal gel, as it loses its colloidal properties, is transformed into a granular precipitated state. These are phenomena that may be observed in the test tube with any colloidal solution such as gelatin.

The progressive accumulation of colloids and their physical alterations with time causes a marked change in the colloidal properties of the intercellular fluid, similar to the changes which may be observed in colloids in the test tube. A precipitation of some colloidal constituents, particularly cholesterol, occurs. Under the microscope changes in the colloidal dispersion of the intercellular fluid are visible as a coarsening of the ground substance, and a granular degeneration of the collagen fiber bundles, and even more strikingly, granulation and fragmentation of the elastic fibers of the intercellular medium.[203,204]

Such changes constitute the background of arteriosclerosis of the medial type so characteristic of aging. The elastic fibers of the arteries are, as elsewhere in the body, inanimate colloidal constituents of the intercellular tissue spaces. Quite independent of the other changes in the intercellular medium of the arteries, such as atheromatous formation, they undergo progressive degeneration with age, causing the arteries to lose their elasticity. Medial sclerosis is a distinct entity apart from atherosclerosis although it is accentuated by lipoid accumulation and degeneration. Since the nutrition of the medial musculo-elastic layer of the arteries is accomplished chiefly by penetration of nutrients directly from the blood stream through the intimal membrane and subintimal space, and only secondarily by the small vasa vasorum capillaries from the outer adventitial coat of the arteries, it is understandable that accumulation of lipoid in the subintimal space forms a mechanical barrier to the flow of nutrients to the muscle cells of the artery thereby causing degeneration. An observation of Horn and Finkel-

stein[34] is of interest in this regard: "Another frequent accompaniment of arteriosclerosis is medial atrophy, which appears to be directly proportional to the thickness of the adjacent (arteriosclerotic) plaque."

That impairment of nutrition to and metabolism of the cellular elements of the arteries actually occurs is indicated by the recent report of Raşka,[205] demonstrating a decrease in respiratory enzyme catalysts in arteriosclerotic aortas. Such decrease in oxidative catalysts is a general indication of impaired metabolism and can be produced experimentally in various organs by interfering with their nutrition.[206] The decrease in respiratory catalysts in arteriosclerotic lesions may in part be due to impaired metabolic activity of the fibroblasts as well as the muscle cells. The functional capacity of fibroblasts decreases markedly with aging, as shown by Du Noüy[207] who found the index of cicatrization, which is largely an index of fibroblastic functional activity, to be a precise measure of physiologic age. This progressive impairment is not due to inherent aging of the fibroblast cells themselves for connective tissue fragments of an old animal placed in young embryonic tissue fluid resume their full functional activities with potential immortality.[208] Aging of the supportive tissue fibroblasts, just as aging of the parenchymal cells, is due to changes in the intercellular medium of the arteries. If, as Leary[2] believes, the fibroblasts in the arterial wall exert lipolytic activity, impairment of this activity with age may accentuate the development of arteriosclerotic lesions. Leary[2] states, "With progressing age the body gradually loses the power to remove excess cholesterol from the arteries. The lipolytic fibroblasts continue to function for some time but with little effect on advanced lesions."

SECONDARY CHANGES IN ARTERIOSCLEROSIS

The primary event in the genesis of atherosclerosis is the deposition of lipoids in the intercellular ground medium just within the endothelial membrane, with subsequent formation of atheromatous lipoid accumulations due to mechanisms which have already been described. The further course of changes in arteriosclerosis is secondary. As suggested, interference with the circulation of tissue fluids in the vascular wall leads to impairment in the metabolic activities of the muscular media and of the fibroblast cells, decreasing their lipolytic activity. These disturbances in the functions of the cellular elements of the vessel wall are indicated by a decrease in oxidative catalysts, and anatomically by muscle atrophy, accentuating the colloidal degenerative changes in the elastic fibers of the media, i.e., medial arteriosclerosis. More important secondary changes occur in the subintima itself where the lipoids initially accumulate. These changes include the heaping up of large aggregates of lipoid in the form of plaques, precipitation of cholesterol crystals and calcium, accumulation of scavenger cells which become laden with lipoid to form foam cells in a futile attempt to remove the lipoid, these cells, together with other elements, undergoing degeneration. As elsewhere in the body where tissue injury occurs, connective tissue reaction and collagen production take place. Another change, also a characteristic reaction to tissue injury elsewhere in the body, is the growth into and around the arteriosclerotic lesions of an abundant network of small blood capillaries. Regarded thus, as a tissue reaction similar to histopathologic changes in other organs, there appears to be no necessity to invest foam cells or vasa vasorum with any special causal attributes in the genesis of arteriosclerosis. The observations of Duff[6] indicating that anisotropic lipoid appears extracellularly in the intima before any fat-containing cells are to be found, and Hueper's similar findings with atheromatosis produced by macromolecular colloidal carbohydrates,[13,14] indicate that foam cells are in fact a secondary phenomenon. Vascularization of atherosclerotic lesions likewise must be regarded as a secondary reactive phenomenon.[33,34]

These secondary changes are ineffectual in accomplishing resolution of the atheromatous accumulations and indeed contribute significantly to the further evolution of arteriosclerotic lesions and their important clinical complications, i.e., narrowing or obstruction of the arterial lumen. As described by Horn and Finkelstein,[34] such complications may develop in several ways. These include progressive narrowing and ultimate occlusion of the lumen by large arteriosclerotic plaques, "thrombosis on a plaque" whose overlying intima is necrotic, degeneration of an arteriosclerotic plaque with rupture of the "atheromatous abscess" through the endothelium and secondary thrombus formation, intramural hemorrhage causing degenerative changes in the intima and ensuing thrombosis on the damaged endothelium, and hematoma of the arterial wall due to hemorrhage in an intramural vessel causing compression of the lumen.

These are the ultimate complications of arteriosclerosis. Unlike the early subendothelial lipoid accumulations, the primary atheroma, they are irreversible changes which cannot disappear. It is obvious that arteriosclerosis in these advanced stages cannot be "cured," and that the problem of arteriosclerosis is principally one of prevention before such irreversible anatomical changes have developed.

REFERENCES

1. Moschkowitz, E. Vascular Sclerosis. New York, 1942. *Oxford University Press.*
2. Leary, T. Cholesterol lysis in atheroma. *Arch. Path.*, 37: 16, 1944.
3. Kube, N. and Ssolowjew, A. Über die Lipoidablagerung in der Aorta von Kindern im frühen Säuglingsalter. *Frankfurt. Ztschr. f. Path.*, 40: 302, 1930.
4. Aschoff, L. Lectures on Pathology. New York, 1924. Paul B. Hoeber, Inc.
5. Krisch, H. Beitrag zur Histologie und Bedeutung der Virchowschen "fettigen Usur" der Aorta. *Virchows Arch. f. path. Anat.*, 230: 191, 1921.
6. Duff, G. L. Nature of experimental cholesterol arteriosclerosis in rabbit. *Arch. Path.*, 22: 161, 1936. Experimental cholesterol arteriosclerosis and its relationship to human arteriosclerosis. *Arch. Path.*, 20: 81, 259, 1935.
7. Groddeck, H. Arteriosklerose. *Ztschr. f. Altersforsch.* 1: 238, 1939.
8. Leary, T. The genesis of atherosclerosis. *Arch. Path.*, 32: 507, 1941.
9. Winternitz, M. C., Thomas, R. M. and Le Compte, P. M. Studies in pathology of vascular disease. *Am. Heart J.*, 14: 399, 1937.
10. Winternitz, M. C., Thomas, R. M. and Le Compte, P. M. The Biology of Arteriosclerosis. Springfield, Ill., 1938. Charles C. Thomas.
11. Fahr-Mannheim, T. Beiträge zur experimentellen Atherosklerose unter besonderer Berücksichtigung der Frage nach dem Zusammenhang zwischen Nebennierenveränderungen und Atherosklerose. *Verhandl. d. deutsch. path. Gesellsch.*, 15: 234, 1912.
12. Hirsch, S. L'atherome aortique des enfants. Études ā propos des debuts de la soi-disant artériosclerose. *Cardiologia*, 5: 122, 1941.
13. Hueper, W. C. Arteriosclerosis. The anoxemia theory. *Arch. Path.*, 39: 117, 1945.
14. Hueper, W. C. The relation between etiology and morphology in degenerative and sclerosing vascular diseases. *Biol. Symposia*, 11: 1, 1945.
15. Aschoff, L. Introduction in Arteriosclerosis. Edited by E. V. Cowdry. New York, 1933. The Macmillan Co.
16. Anitschkow, N. Zur Histophysiologie der Arterienwand. *Klin. Wchnschr.*, 4: 2233, 1925.
17. Anitschkow, N. Das Wesen und die Entstehung der Atherosklerose. *Ergebn. d. inn. Med. u. Kinderh.*, 28: 1, 1925.
18. Anitschkow, N. Experimental Arteriosclerosis in Animals. Chapt. 10 in Arteriosclerosis. Edited by E. V. Cowdry. New York, 1933. The Macmillan Co.
19. Bruger, M. and Poindexter, C. A. Relation of plasma cholesterol to obesity and to some of the complicating degenerative diseases (diabetes mellitus, essential hypertension, osteo-arthritis and arteriosclerosis). *Arch. Int. Med.*, 53: 423, 1934.
20. Weinhouse, S. and Hirsch, E. F. Atherosclerosis; lipids of serum and tissues in experimental atherosclerosis of rabbits. *Arch. Path.*, 30: 856, 1940.
21. Hirsch, E. F. and Weinhouse, S. Role of lipids in atherosclerosis. *Physiol. Rev.*, 23: 185, 1943.
22. Page, I. H. Some aspects of nature of chemical changes occurring in atheromatosis. *Ann. Int. Med.*, 14: 1741, 1941.
23. McArthur, C. S. The acetone-soluble lipid of the atheromatous aorta. *Biochem. J.*, 36: 559, 1942.
24. Gibbs, C. B. F., Buckner, E. and Bloor, W. R. Cholesterol to cholesterol ester ratio in plasma of diabetics with advanced arteriosclerosis. *New England J. Med.*, 209: 384, 1933.
25. White, P. Diabetes in children. *Bull. New York Acad. Med.*, 10: 347, 1934.
26. Rabinowitch, I. M. Arteriosclerosis in diabetes; relationship between plasma cholesterol and arteriosclerosis; effects of high carbohydrate, low calorie diet. *Ann. Int. Med.*, 8: 1436, 1935.
27. Lisa, J. R., Magiday, M., Galloway, I. and Hart, J. F. Arteriosclerosis with diabetes mellitus; study of pathologic findings in 193 diabetic and 2,250 non-diabetic patients. *J. A. M. A.*, 120: 192, 1942.
28. Riebold, G. Dauernde erhebliche Blutdrucksteig-

erung als Frühsymptom einer Gehirnarteriosklerose. *München. med. Wchnschr.*, 64: 1390, 1917.

29. Sigler, L. H. Spontaneous nonrhythmic variations in blood pressure levels and in "silent gap"; theory of vasomotor arrhythmia. *Am. J. M. Sc.*, 177: 494, 1929.
30. Raab, W. Hirnblutuntersuchungen bei Hypertonie. *Ztschr. f. klin. Med.*, 115: 577, 1931.
31. Bordley, J., III and Baker, B. M., Jr. Arteriosclerosis of cerebral vessels and pathogenesis of hypertension. *Bull. Johns Hopkins Hosp.*, 39: 229, 1926.
32. Katz, L. N. and Dauber, D. V. Pathogenesis of atherosclerosis. J. Mt. Sinai Hosp., 12: 382, 1945.
33. Leary, T. Vascularization of atherosclerotic lesions. *Am. Heart J.*, 16: 549, 1938.
34. Horn, H. and Finkelstein, L. E. Arteriosclerosis of coronary arteries and mechanism of their occlusion. *Am. Heart J.*, 19: 655, 1940.
35. Altschul, R. Histologic analysis of arteriosclerosis. *Arch. Path.*, 38: 305, 1944.
36. Ramsay, E. M. Studies in pathology of vascular disease; nutrition of blood vessel wall: review of literature. *Yale J. Biol. & Med.*, 9: 43, 1936.
37. Petroff, J. R. Über die Vitalfärbung der Gefässwandungen. *Beitr. z. path. Anat.*, 71: 115, 1922–1923.
38. Lange, F. Studien zur Pathologie der Arterien, insbesondere zur Lehre von der Arteriosklerose. *Virchows Arch. f. path. Anat.*, 248: 463, 1924.
39. Iwanov, G. Die lymphgefässe der Wände der Blutgefässe—Vasa lymphatica vasorum sanguinorum (zur Methodik ihrer Injektion). *Ztschr. f. Anat. u. Entwcklngsgesch.*, 99: 669, 1933.
40. Wolkoff, K. and Hesse, E.[16]
41. Faber, M. The cholesterol content of the human aorta in relation to the serum cholesterol concentration. *Acta med. Scandinav.*, 125: 418, 1946.
42. Hunter, A. Blood pressure among standard lives. *J. Inst. Actuaries*, 70: 60, 1939.
43. Daley, R. M., Ungerleider, H. E. and Gubner, R. S. Prognosis in hypertension. *J. A. M. A.*, 121: 383, 1943.
44. Anrep, G. V., Davis, J. C. and Volhard, E. Effect of pulse pressure upon coronary blood flow. *J. Physiol.*, 73: 405, 1931.
45. Gregg, D. E. The phasic variations in coronary flow, studied by autoperfusion method. Proc. Am. Physiol. Soc., 46th Annual Meet., New York, March 28–31, 1934. *Am. J. Physiol.*, 109: 44, 1934.
46. Johnson, J. R. and Di Palma, J. R. Intramyocardial pressure and its relation to aortic blood pressure. *Am. J. Physiol.*, 125: 234, 1939.
47. Gregg, D. E. Phasic changes in flow through different coronary branches. Chapter in Blood, Heart and Circulation. *Am. Assoc. Adv. Sc.*, 81, 1940.
48. Ehrich, W., de la Chapelle, C. E. and Cohn, A. E. Anatomical ontogeny; man; study of coronary arteries. *Am. J. Anat.*, 49: 241, 1931.
49. Davson, H. and Danielli, J. F. The Permeability of Natural Membranes. New York, 1943. The Macmillan Co.
50. Chambers, R. and Zweifach, B. W. Capillary endothelial cement in relation to permeability. *J. Cell. & Comp. Physiol.*, 15: 255, 1940.
51. Lange, K. Capillary permeability in myxedema. *Am. J. M. Sc.*, 208: 5, 1944.
52. Shapiro, S. Relation of certain glands of internal secretion to development of atherosclerosis. *Endocrinology*, 11: 279, 1927.
    Influence of thyroidectomy, splenectomy, gonadectomy, and suprarenalectomy upon the development of experimental atherosclerosis in rabbits. *J. Exper. Med.*, 45: 595, 1927.
53. Steiner, A. and Kendall, F. E. Atherosclerosis and arteriosclerosis in dogs following ingestion of cholesterol and thiouracil. *Arch. Path.*, 42: 433, 1946.
54. Murata, M. and Kataoka, S. Experimentelle Arteriosklerose und Schilddrüsenfütterung. *Verhandl. d. Jap. path. Gesellsch.*, 8: 221, 1918.
55. Liebig, H. Die Beeinflüssung der experimentellen Atherosklerose durch Jodbehandlung. *Arch. f. exper. Path. u. Pharmakol.*, 159: 265, 1931.
56. Turner, K. B. and Khayat, G. B. Studies on prevention of cholesterol atherosclerosis in rabbits; influence of thyroidectomy upon protective action of potassium iodide. *J. Exper. Med.*, 58: 127, 1933.
57. Friedland, I. B. Untersuchungen über den Einfluss der Schilddrüsenprepärate auf die experimentelle Hypercholesterinäme und Atherosklerose. *Ztschr. f. d. ges. exper. Med.*, 87: 683, 1933.
58. Turner, K. B. Studies on prevention of cholesterol atherosclerosis in rabbits; effects of whole thyroid and of potassium iodide. *J. Exper. Med.*, 58: 115, 1933.
59. Page, I. H. and Bernhard, W. G. Cholesterol-induced atherosclerosis; its prevention in rabbits by feeding of organic iodine compound. *Arch. Path.*, 19: 530, 1935.
60. Malisoff, W. M. Prevention of atherosclerosis in rabbits; administration of potassium thiocyanate. *Proc. Soc. Exper. Biol. & Med.*, 35: 356, 1936.
61. Hueper, W. C. Experimental studies on the therapy and prevention of degenerative vascular diseases. I. The effects of medication with potassium thiocyanate on experimental cholesterol atheromatosis. *Arch. Path.*, 38: 93, 1944.
62. Meeker, D. R., Kesten, H. D. and Jobling, J. W. Effect of iodine on cholesterol-induced atherosclerosis. *Arch. Path.*, 20: 337, 1935.
63. Davis, D., Stern, B. and Lesnick, G. Lipid and cholesterol content of blood of patients with angina pectoris and arteriosclerosis. *Ann. Int. Med.*, 11: 354, 1937.
64. Steiner, A. and Domanski, B. Serum cholesterol level in coronary arteriosclerosis. *Arch. Int. Med.*, 71: 397, 1943.
65. Landé, K. E. and Sperry, W. M. Human atherosclerosis in relation to cholesterol content of blood serum. *Arch. Path.*, 22: 301, 1936.
66. Morrison. L. M., Hall, L. and Cheney, A. L. Cholesterol metabolism: blood serum cholesterol and ester levels in 200 cases of acute coronary thrombosis. *Am. J. M. Sc.*, 216: 32, 1948.
67. Lerman, J. and White, P. D. Metabolic changes in young people with coronary heart disease. *J. Clin. Investigation*, 25: 914, 1946.

68. Underdahl, L. O. and Smith, H. L. Coronary artery disease in women under the age of forty. *Proc. Staff Meet., Mayo Clin.*, 22: 479, 1947.
69. Dock, W. Personal communication.
70. Kuczynski, B. Pathologisch-geographische Untersuchungen in der kirgisisch-dsungarischen Steppe. *Klin. Wchschr.*, 4: 39, 1925.
71. Rosenthal, S. R. Studies in atherosclerosis: chemical, experimental and morphologic; rôles of cholesterol metabolism, blood pressure and structure of aorta; fat angle of aorta (F. A. A.) and infiltration-expression theory of lipoid deposit. *Arch. Path.*, 18: 473, 660, 1934. Studies in atherosclerosis: chemical, experimental and morphologic; possible dangers of iodine therapy in atherosclerosis of aorta seen from experimental standpoint. *Arch. Path.*, 18: 827, 1934.
72. Dillon, J. A. and Evans, L. R. Primary amyloidosis; report of 3 cases. *Ann. Int. Med.*, 17: 722, 1942.
73. Leupold, E. Untersuchungen über die Mikrochemie und Genese des Amyloids. *Beitr. z. path. Anat. u. z. allg. Path.*, 64: 347, 1917.
74. Nakonetschny, A. Über die pathologischen Arterienveränderungen in der Milz. *Virchows Arch. f. path. Anat.*, 245: 564, 1923.
75. Hueper, W. C. and Ichniowski, C. T. Toxicopathologic studies on dye T-1824. *Arch. Surg.*, 48: 17, 1944.
76. Zettler, L. Die Wirkung von Gefässmitteln auf die Permeabilität der Arterien. *Arch. f. exper. Path. u. Pharmakol.*, 185: 141, 1937.
77. Petroff, J. R. Über die Vitalfärbung der Gefässwandungen. *Beitr. z. path. Anat.*, 71: 115, 1922–1923.
78. Okuneff, N. Vital dye imbibition of aorta wall. *Virchows Arch. f. path. Anat.*, 269: 685, 1926.
79. Bruger, M. State of cholesterol and nature of cholesterol-protein complex in pathological body fluids. *J. Biol. Chem.*, 108: 463, 1935.
80. Moreton, J. R. Atherosclerosis and alimentary hyperlipemia. *Science*, 106: 190, 1947.
81. Schönholzer, G. Zur Frage des cholesterolytischen Vermögens des Blutserums. *Helvet. med. acta*, 6: 692, 1939.
82. Blix, G., Tiselius, A. and Svensson, H. Lipids and polysaccharides in electrophoretically separated blood serum proteins. *J. Biol. Chem.*, 137: 485, 1941.
83. Went, S. and Goreczky, L. Die Verteilung der Serumphosphatide und des Cholesterins in durch Filtration durch grossporige Kollodiumfilter gewonnenen Serumultrafiltraten. *Biochem. Ztschr.*, 239: 441, 1931.
84. Man, E. B. and Peters, J. P. Permeability of capillaries to plasma lipoids. *J. Clin. Investigation*, 12: 1031, 1933.
85. Bruger, M. The lipiduria of Bright's disease: observations on the urinary excretion of cholesterol, lipid phosphorus and fatty acids. *J. Clin. Investigation*, 15: 464, 1936.
86. Bing, J. and Starup, U. Investigations on hyperlipaemia and cholesterinuria. *Acta med. Scandinav.*, 86: 12, 1935.
87. Fishberg, A. M. Hypertension and Nephritis. P. 384, 4th ed. Philadelphia, 1939. Lea & Febiger.
88. Kujath, G. Zur Frage der differential-diagnostischen Bedeutung des Liquor-cholesterins. *Allg. Ztschr. f. Psychiat.*, 121: 249, 1943.
89. Degkwitz, R. Cholesterin und Lecithin im Wasser- und Säure-Basenhaushalt. *Klin. Wchnschr.*, 9: 2336, 1930.
90. Cook, R. P. Cholesterol metabolism. *Nutrition Abstr. & Rev.*, 12: 1, 1942.
91. Wells, H. G. The Chemistry of Arteriosclerosis. Chapter 11 in Arteriosclerosis. Edited by E. V. Cowdry. New York, 1933. The Macmillan Co.
92. Loeper, M., Lemaire, A. and Lesure, A. Le pouvoir cholestérolytique du sérum humain normal et pathologique. *Compt. rend. Soc. de biol.*, 98: 101, 1928.
93. Eck, M. and Desbordes, J. Influence de l'age sur les variations de la cholestérinémie et du pouvoir cholestérolytique. *Compt. rend. Soc. de biol.*, 118: 498, 1935. Sur le taux de la cholestérine et la pouvoir cholestérolytique du sérum de vieillard. *Compt. rend Soc. de biol.*, 117: 428, 1934.
94. Alvarez, C. and Neuschlosz, S. M. Untersuchungen über das Blutcholesterin bei arteriellen Hochdruck. *Klin. Wchnschr.*, 10: 244, 1931.
95. Longsworth, L. G., Shedlovsky, T. and MacInnes, D. A. Electrophoretic patterns of normal and pathological human blood serum and plasma. *J. Exper. Med.*, 70: 399, 1939.
96. Bloch, K. and Rittenberg, D. On the utilization of acetic acid for cholesterol formation. *J. Biol. Chem.*, 145: 625, 1942.
97. Rittenberg, D. The William Henry Welch lectures. The application of isotope technique to problems of biology and medicine. *J. Mt. Sinai Hosp.*, 14: 891, 1947–1948.
98. Bloch, K., Berg, B. N. and Rittenberg, D. Biological conversion of cholesterol to cholic acid. *J. Biol. Chem.*, 149: 511, 1943.
99. Sobotka, H. Physiological Chemistry of the Bile. Baltimore, 1937. Williams and Wilkins.
100. Wright, A. Cholesterol and cholesterol esters in dog bile; quantitative methods. *J. Exper. Med.*, 59: 407, 1934.
101. Schramm, G. and Wolff, A. Über die Cholesterinesterasen und ihre Beziehungen zur Fettresorption und zum Fettransport. *Ztschr. f. physiol. Chem.*, 263: 61, 1940. Über die enzymatische Veresterung einige Steroide. ibid. 263: 73, 1940. Cited by Weinhouse, S. in Blood Cholesterol. *Arch. Path.*, 35: 438, 1943.
102. Bloor, W. R. Biochemistry of the Fatty Acids. New York, 1943. Reinhold Publishing Corp.
103. Member, S., Bruger, M. and Oppenheim, E. Experimental atherosclerosis; effects of various bile acids on cholesterol levels. *Arch. Path.*, 38: 210, 1944.
104. Cook, R. P. Cholesterol feeding and fat metabolism. *Biochem. J.*, 30: 1630, 1936.
105. Artom, C., Sarzana, G., Perrier, C., Santangelo, M. and Segrè, E. Synthèse des phospholipides au cours de l'absorption des graisses. *Arch. internat. de physiol.*, 45: 32, 1937.
106. Fries, B. A., Ruben, S., Perlman, I. and Chaikoff, I. L. Radioactive phosphorus as indicator of phospholipid metabolism; role of stomach, small intestine, and large intestine in phospholipid

metabolism in presence and absence of ingested fat. *J. Biol. Chem.*, 123: 587, 1938.

107. VERZÁR, F. and LASZT, L. Hemmung der Fettresorption durch Monojodessigsäure und Phlorrhizin. *Biochem. Ztschr.*, 270: 35, 1934.
108. SINCLAIR, R. G. Blood phospholipid as transport mechanism. *J. Biol. Chem.*, 115: 211, 1936.
109. PETERS, J. P. and VAN SLYKE, D. D. Quantitative Clinical Chemistry. Vol. I, Interpretations, 2nd ed. Baltimore, 1946. Williams and Wilkins.
110. BALLOU, G. A., BOYER, P. D. and LUCK, J. M. Electrophoretic mobility of human serum albumin as affected by lower fatty acid salts. *J. Biol. Chem.*, 159: 111, 1945.
111. LUETSCHER, J. A., JR. Electrophoretic analysis of plasma and urinary proteins. *J. Clin. Investigation*, 19: 313, 1940.
112. LEWIS, L. A. and MCCULLAGH, E. P. Electrophoretic analysis of plasma proteins in hyperthyroidism and hypothyroidism. *Am. J. M. Sc.*, 208: 727, 1944.
113. CHARGAFF, E., ZIFF, M. and MOORE, D. H. Studies on chemistry of blood coagulation; electrophoretic study of effect of anticoagulants on human plasma complement. *J. Biol. Chem.*, 139: 383, 1941.
114. HAHN, P. F. Abolishment of alimentary lipema following injection of heparin. *Science*, 98: 19, 1943.
115. BOXER, G. E. and STETTEN, DEW., JR. Effect of dietary choline upon rate of turnover of phosphatide choline. *J. Biol. Chem.*, 153: 617, 1944.
116. FORBES, J. C. Effect of thyroxine on neutral fat and cholesterol content of body and liver of rats. *Endocrinology*, 35: 126, 1944.
117. KARTIN, B. L., MAN, E. B., WINKLER, A. W. and PETERS, J. P. Blood ketones and serum lipids in starvation and water deprivation. *J. Clin. Investigation*, 23: 824, 1944.
118. KESTEN, H. D. and SILBOWITZ, R. Experimental atherosclerosis and soya lecithin. *Proc. Soc. Exper. Biol. & Med.*, 49: 71, 1942.
119. ADLERSBERG, D. and SOBOTKA, H. Effect of prolonged lecithin feeding on hypercholesterolemia. *J. Mt. Sinai Hosp.*, 9: 955, 1943.
120. HERRMANN, G. R. Cholesterol levels in various diseases and effects of decholesterizing agents. *Texas State J. Med.*, 42: 260, 1946.
121. STEINER, A. and DOMANSKI, B. Effect of feeding of "soya lecithin" on serum cholesterol level of man. *Proc. Soc. Exper. Biol. & Med.*, 55: 236, 1944.
122. BÜRGER, M. and WINTERSEEL, W. Sterinausscheidung und Sterinbalanz bei totalem Gallengangsverschlusz. *Ztschr. f. d. ges. exper. Med.*, 66: 459, 1929; cited by Weinhouse, S.: Blood Cholesterol. *Arch. Path.*, 35: 438, 1943.
123. FLEISCHMANN, W. and SHUMACKER, H. B., JR. The relationship between serum cholesterol and total body cholesterol in experimental hyper- and hypothyroidism. *Bull. Johns Hopkins Hosp.*, 71: 175, 1942.
124. BOYD, E. M. Lipid content of white blood cells in normal young women. *J. Biol. Chem.*, 101: 623, 1933.
125. BOYD, E. M. Reaction of lipids in blood leucocytes to fever and infection. *Surg., Gynec. & Obst.*, 60: 205, 1935.
126. OKEY, R. Middle and old age in cholesterol-fed rats. *Proc. Soc. Exper. Biol. & Med.*, 46: 466, 1941.
127. OKEY, R. and BOYDEN, R. E. Studies of metabolism of women; variations of lipid content of blood in relation to menstrual cycle. *J. Biol. Chem.*, 72: 261, 1927.
128. BUNTING, C. H. and HUSTON, J. Fate of the lymphocyte. *J. Exper. Med.*, 33: 593, 1921.
129. SCHOENHEIMER, R. Über eine Störung der Cholesterin ausscheidung. (Ein Beitrag zur Kenntnis der Hypercholesterinämien). *Ztschr. f. klin. Med.*, 123: 749, 1933.
130. RUZICKA, L. and PRELOG, V. Isolation of cholestenone from pig testes. *Helvet. Chim. Acta*, 26: 975, 1943. Isolation of cholestenone from pig spleen. *Helvet. chim. acta*, 26: 2222, 1943.
131. GILMAN, A. The effects of drugs on nerve activity. *Ann. New York Acad. Sc.*, 47: 549, 1946.
132. ANNEGERS, J. H., SNAPP, F. E., IVY, A. C. and ATKINSON, A. J. Effect of cinchophen on secretion of cholic acid. *Arch. Int. Med.*, 73: 1, 1944.
133. ASKANAZY, S. Rhodan-Kalzium-Diuretin gegen Hypertonie. *München med. Wchnschr.*, 74: 1793, 1927.
134. LINDBERG, H. A., WALD, M. H. and BARKER, M. H. Observations on pathologic effects of thiocyanate: experimental study. *Am. Heart J.*, 21: 605, 1941.
135. WESTPHAL, K. and BLUM, R. Die Rhodentherapie des genuinen arteriellen Hochdrucks und ihre theoretische Begründung. *Deutsches Arch. f. klin. Med.*, 152: 331, 1926.
136. HUEPER, W. C. Experimental studies on the therapy and prevention of degenerative vascular diseases. I. The effects of medication with potassium thiocyanate on experimental cholesterol atheromatosis. *Arch. Path.*, 38: 93, 1944.
137. GOEBEL, F. Sur l'influence du système végétatif sur la teneur du sang en cholestérine. *J. de physiol. et de path. gén.*, 30: 340, 1932.
138. HILL, E. and KOEHLER, A. E. Effect of epinephrine on lipid excretion. *J. Biol. Chem.*, 98: 185, 1932.
139. ASHE, B. I. and BRUGER, M. Cholesterol content of plasma in chronic nephritis and retention uremia. *Am. J. M. Sc.*, 186: 670, 1933.
140. BRUGER, M. and POINDEXTER, C. A. Effect of ingestion of water and of urea on cholesterol content of plasma. *J. Biol. Chem.*, 101: 21, 1933.
141. MAYER, A. and SCHAEFFER, G. Variations de la teneur des tissus en lipoides et en eau au cours de l'inanition absolue. *J. de physiol. et de path. gén.*, 16: 203, 1914–1915.
142. KOUNTZ, W. B., SONNENBERG, A., HOFSTATTER, L. and WOLFF, G. Blood cholesterol levels in elderly patients. I. Relation of age, sex, basal metabolic rate, cardiac decompensation, and Coronary and peripheral sclerosis to blood cholesterol levels in the aged. *Biol. Symposia*, 11: 79, 1945.
143. HEYMANN, W. and RACK, F. Independence of serum cholesterol from exogenous cholesterol in infants and children. *Am. J. Dis. Child.*, 65: 235, 1943.
144. GOUGH, N. Effect of diet on concentration of cho-

lesterol in blood and bile. *Brit. M. J.*, 2: 390, 1943.

145. Cook, R. P. Cholesterol feeding and fat metabolism. *Biochem. J.*, 30: 1630, 1936.
146. Eckstein, H. C. Sterol metabolism in young white rats; effect of saponifiable lipids and degree of unsaturation of lipids on sterol metabolism of white rat. *J. Biol. Chem.*, 125: 99, 1938. Sterol metabolism in young white rats; effect of high and low fat diets on sterol balances and sterol content of hair of young white rats. *J. Biol. Chem.*, 125: 107, 1938.
147. Papenkort, E. Über den Einfluss der Fettbelastung auf Resorption und Ausscheidung der Gallensäuren beim Menschen. *Ztschr. f. d. ges. exper. Med.*, 93: 249, 1934.
148. Kempner, W. Some effects of rice diet treatment of kidney disease and hypertension. *Bull. New York Acad. Med.*, 22: 358, 1946.
149. Gardner, J. A. and Gainsborough, H. Blood cholesterol studies in biliary and hepatic disease. *Quart. J. Med.*, 23: 465, 1930.
150. Gardner, J. A., Gainsborough, H. and Murray, R. M. Distribution of sterols in human faeces; examination of ileal contents. *Biochem. J.*, 29: 1139, 1935.
151. Sperry, W. M. Lipid excretion; study of relationship of bile to fecal lipids with special reference to certain problems of sterol metabolism. *J. Biol. Chem.*, 71: 351, 1927.
152. Beumer, H. and Hepner, F. Über die Ausscheidungswege des Cholesterins. *Ztschr. f. d. ges. exper. Med.*, 64: 787, 1929.
153. Roffo, A. H. Descolesterinización por el Alcaucil (Cynara Scolymus). *Bol. Inst. de med. exper. para el estud. y trat. de cáncer*, 20: 65, 1943.
154. Roffo, A. H. Egg-plant (Solanum melongena L.) in decholesterolization. *Yale J. Biol. & Med.*, 18: 25, 1945.
155. Snell, A. M. Tropical and nontropical sprue (chronic idiopathic steatorrhea): their probable interrelationship. *Ann. Int. Med.*, 12: 1632, 1939.
156. Roy, A. and Sen, P. B. Effect of quinine on absorption of fat. *Ann. Biochem. & Exper. Med.*, 3: 9, 1943.
157. Frazer, A. C. Lipolysis and fat absorption. *J. Physiol.*, 102: 329, 1943.
158. Burr, G. O. and Barnes, R. H. Non-caloric functions of dietary fats. *Physiol. Rev.*, 23: 256, 1943.
159. Curtis, A. C. and Kline, E. M. Influence of liquid petrolatum on blood content of carotene in human beings. *Arch. Int. Med.*, 63: 54, 1939.
160. Dam, H. Formation of coprosterol in intestine: action of intestinal bacteria on cholesterol. *Biochem. J.*, 28: 820, 1934.
161. Dubos, R. J. Personal communication.
162. Rosenheim, O. and Webster, T. A. Mechanism of coprosterol in vivo; its inhibition by succinyl sulphathiazole and by carbarsone. *Biochem. J.*, 37: 580, 1943.
163. Anchel, M. and Schoenheimer, R. Deuterium as indicator in study of intermediary metabolism; further studies in coprosterol formation. Use of compounds containing labile deuterium for biological experiments. *J. Biol. Chem.*, 125: 23, 1938.
164. Schmidt, L. H. and Hughes, H. B. Studies on bile acid metabolism; fate of cholic acid in guinea pig. *J. Biol. Chem.*, 143: 771, 1942.
165. Schmidt, L. H., Hughes, H. B., Green, M. H. and Cooper, E. Studies on bile acid metabolism; action of Alcaligenes faecalis on cholic acid. *J. Biol. Chem.*, 145: 229, 1942.
166. Hughes, H. B. and Schmidt, L. H. Oxidation of steroids by Alcaligenes faecalis. *Proc. Soc. Exper. Biol. & Med.*, 51: 162, 1942.
167. Hoehn, W. M., Schmidt, L. H. and Hughes, H. B. Studies on bile acid metabolism; separation and identification of ketocholanic acids formed during oxidation of cholic acid by Alcaligenes faecalis. *J. Biol. Chem.*, 152: 59, 1944.
168. Schmidt, L. H. and Hughes, H. B. Conversion of hydroxy-steroids to keto-steroids. *U. S. P.* 2: 360, 447, 1944. Cited by Turfitt, G. E. Microbiological agencies in the degradation of steroids. II. Steroid utilization by the microflora of soils. *J. Bact.*, 54: 557, 1947.
169. Schoenheimer, R., Rittenberg, D., and Graff, M. Deuterium as indicator in study of intermediary metabolism; mechanism of coprosterol formation. *J. Biol. Chem.*, 111: 183, 1935.
170. Herter, C. A. and Kendall, A. I. Influence of dietary alternations on the types of intestinal flora. *J. Biol. Chem.*, 7: 203, 1909–1910.
171. Wollstein, M. Influence of high protein feeding on the general metabolism, on the intestinal flora and on the body temperature of infants. Part 3. Bacteriological observations. *Am. J. Dis. Child.*, 4: 279, 1912.
172. Torrey, J. C. Regulation of the intestinal flora of dogs through diet. *J. M. Res.*, 39: 415, 1918–1919.
173. Rosenheim, O. and Webster, T. A. Dietary factor concerned in coprosterol formation. *Biochem. J.*, 35: 920, 1941.
174. Rosenheim, O. and Webster, T. A. Mechanism of coprosterol formation in vivo; cholestenone as intermediate. *Biochem. J.*, 37: 513, 1943.
175. Rosenheim, O. and Starling, W. W. Oxycholesterol. *Chem. Ind.*, 52: 1056, 1933.
176. Sobotka, H. Chemistry of Steroids. Baltimore, 1938. Williams & Wilkins Co.
177. Diels, O. and Abderhalden, E. Zur Kenntniss des Cholesterins. *Ber. d. deutsch. chem. Gesellsch.*, 37: 3092, 1904.
178. Schoenheimer, R. and Evans, E. A., Jr. Allocholesterol and epiallocholesterol. *J. Biol. Chem.*, 114: 567, 1936.
179. Wolkoff, K. Zur Frage der Morphologie der Lipoidablagerungen im Organismus der Teermäuse bei verschiedener Nahrungsart. *Ztschr. f. Krebsforsch.*, 31: 291, 1930.
180. Ssolowjew, A. Experimentelle Untersuchungen über die Bedeutung von lokaler Schädigung für die Lipoidablagerung in der Arterienwand. *Ztschr. f. d. ges. exper. Med.*, 69: 94, 1929–1930.
181. Schlichter, J. G. Vascularization of the aorta in different species in health and disease. Am. Soc. Study of Arteriosclerosis, 2nd meet., Chicago, November 2, 1947. *Am. Heart J.*, 35: 850, 1948.
182. Wilens, S. L. Distribution of intimal atheromatous lesions in arteries of rabbits on high cholesterol diets. *Am. J. Path.*, 18: 63, 1942.

183. Wartman, W. B. Incidence and severity of arteriosclerosis in organs from 500 autopsies. *Am. J. M. Sc.*, 186: 27, 1933.
184. Page, I. H. Arteriosclerosis and lipid metabolism. *Biol. Symposia*, 11: 43, 1946.
185. Westenhöfer, P. Über die Lokalisation und phylogenetische Grundlage der Verfettungen und Sklerosen der Aorta und ihre Aeste. *Deutsche med. Wchnschr.*, 48: 518, 1922.
186. Meeker, D. R. and Jobling, J. W. Chemical study of arteriosclerotic lesions in human aorta. *Arch. Path.*, 18: 252, 1934.
187. Schönheimer, R. Zur Chemie der gesunden und der atherosklerotischen Aorta. Ueber die quantitativen Verhältnisse des Cholesterins und der Cholesterinester. *Ztschr. f. physiol. Chem.*, 160: 61, 1926.
188. Christianson, O. O. Observations on lesions produced in arteries of dogs by injection of lipids; lipids injected: human fat, fatty acids, soaps and cholesterol. *Arch. Path.*, 27: 1011, 1939.
189. Simms, H. S., Parshley, M. S. and Pitt, R. B. Fat deposition in vitro caused by lipfanogens and opposed by antilipfanogen. *J. Gerontol.*, 2: 205, 1947.
Simms, H. S., Parshley, M. S., Pitt, R. B. and Fulton, J. B. Further studies on the fat-depositing mechanism. *Am. Heart J.*, 36: 469, 1948.
190. Dock, W. Predilection of atherosclerosis for coronary arteries. *J. A. M. A.*, 131: 875, 1946.
191. Zinserling, W. D. Cited by Hueper, W. C. in Arteriosclerosis. The anoxemia theory. *Arch. Path.*, 39: 187, 1945.
192. Bürger, M. and Schlomka, G. Ergebnisse und Bedeutung chemischer Gewebsuntersuchungen für die Alternsforschung. *Klin. Wchnschr.*, 7: 1944, 1928.
193. Troitzkaja-Andreewa, A. M. Zur Kenntnis der Altersveränderungen der Arterien. (Über die Altersfibrose der Arterienwand.) *Frankfurt. Ztschr. f. Path.*, 41: 120, 1931.
194. Wetzel, G. Altersanatomie. *Verhandl. d. anat. Gesellsch.*, 41: 15, 1932.
195. Herxheimer, G. Ueber das Verhalten der kleinen Gefässe der Milz. *Berl. klin. Wchnschr.*, 54: 82, 1917.
196. Baldauf, L. K. Chemistry of atheroma and calcification (Aorta). *J. M. Res.*, 15: 355, 1906.
197. Schönheimer, R. Zur Chemie der gesunden und der atherosklerotischen Aorta. Ueber die quantitativen Verhältnisse des Cholesterins und der Cholesterinester. *Ztschr. f. physiol. Chem.*, 160: 61, 1926.
198. Bensley, S. H. On presence, properties and distribution of intercellular ground substance of loose connective tissue. *Anat. Rev.*, 60: 93, 1934.
199. Rocosolano, A. de G. A physico-chemical hypothesis of aging. *Kolloidchem. Beihefte*, 19: 441, 1924.
200. Ruzicka, V. Beiträge zum Studium der Protoplasmahysteresis und der hysteretischen Vorgänge. (Zur Kausalität des Alterns.) *Arch. f. mikr. Anat. u. Entwick.*, 101: 459, 1924.
201. Dhar, N. R. Senescence inherent property of animal cells. *Quart. Rev. Biol.*, 7: 68, 1932.
202. Schrödinger, E. What is Life? New York, 1946. The Macmillan Co.
203. Weidman, F. Aging of the skin, in Problems of Aging, ed. by E. V. Cowdry. Baltimore, 1939. Williams & Wilkins Co.
204. Ejiri, I. Histology of human skin: II. On differences in the elastic fibers of the skin according to sex and age. *Japan J. Dermat. & Urol.*, 40: 216, 1936; abstracted, *Arch. Dermat. & Syph.*, 37: 664, 1938.
205. Raska, S. B. Discussion in Experimental Hypertension, A Symposium. *New York Academy Sc.* Special publication. 3: 50, 1946.
206. Raska, S. B. Metabolism of kidney in experimental renal hypertension; concentration of cytochrome c and activities of cytochrome oxidase and of succinic dehydrogenase systems in kidney of dogs with experimental renal hypertension. Inhibitory effect of renin and of kidney tissue preparations from hypertensive dogs on respiratory enzymes. *J. Exper. Med.*, 82: 227, 1945.
207. Du Nouy, P. L. Biological Time. New York, 1937. The Macmillan Co.
208. Carrel, A. The relation of cells to one another. Chap. 9 in Human Biology and Racial Welfare. Ed. by E. V. Cowdry. New York, 1930. Paul B. Hoeber, Inc.

Seminars on Congestive Failure

The Mechanism of Heart Failure*

A Resume of Physiologic Factors in Cardiovascular Failure

ROBERT PAINE, M.D.† AND JOHN R. SMITH, M.D.
St. Louis, Missouri

WITHIN recent years many informative observations concerning the mechanism of cardiac failure have been added to the record. A number of these studies entailed animal experiments from which indirect though valuable data regarding heart disease in man may be derived. Many of the recent studies included observations of cardiac performance in normal individuals and in patients with heart disease. In the latter instances technical refinements were utilized permitting the observation of certain intracardiac and intravascular pressure relationships and an accurate determination of cardiac output. Although the pathologic physiology of heart failure has been widely investigated, the employment of newer methods in the study of cardiovascular physiology in man has recreated a lively interest in the problem. At present new ideas are advanced in rapid succession and many older concepts are being revised. It may be of some value to reexamine the question of the genesis of cardiac failure in the light of valuable evidence from clinical and experimental observations now at hand.

MYOCARDIAL INJURY

It is quite admissible that failure of the heartarises in consequence of primary injury to the myocardium. The association of clinical heart failure with coronary disease, hypertrophy of the muscle fibers and other morphologic changes of acquired and congenital lesions is so familiar that further comment is unnecessary. However, the means by which myocardial damage invokes failure of the organ is poorly understood.[39] It seems probable that adequate knowledge of the fundamental myocardial defects must be contingent upon a more thorough understanding of muscle physiology.[66]

Attempts to produce heart failure under experimental conditions have met with some success. Using the heart-lung preparation, the administration of chloral hydrate, chloroform, potassium chloride or other agents which are noxious to the myocardium[34,45,124] impairs the mechanical efficiency of the ventricles[34] causing dilatation of the heart, a rise in left and right intra-auricular pressures and a decrease in minute volume output of the ventricles. Similar results have been obtained in heart-lung preparations by the use of vasoconstricting drugs to reduce coronary flow[123,136] or by ligation of the coronary arteries.[124] In the study of circulatory dynamics use of the heart-lung preparation has offered certain fundamental suggestions of myocardial function;[101] however, the usefulness of such

* From the Cardio-Vascular Division, Department of Medicine, Washington University School of Medicine, St. Louis.
† Rockefeller Fellow in Cardiology 1948–49.

preparations is restricted and the qualitative nature of the myocardial injury producing heart failure is self-evident.

On the other hand, the use of the heart-lung[105,124] and isolated heart preparations[94] have brought forward data on the energy metabolism of the normal and failing heart. Under normal conditions the heart performs increased mechanical work by virtue of its propensity to dilate optimally (i.e., by increasing initial fiber length). The performance of greater work and increased diastolic size is attended by an augmentation of oxygen consumption.[32,124] Starling and Visscher[124] showed that the oxygen consumption of the heart varied with the initial length of its muscle fibers. Furthermore, convincing evidence has been evolved[94,105] to show that as the heart becomes fatigued (and eventually fails), dilatation of the ventricles exceeds the limit normally required for optimum energy liberation. Oxygen consumption is further augmented. In spite of the greater dilatation and increased oxygen utilization the work output falls off and the mechanical efficiency of the heart becomes curtailed. These considerations are of great interest in the matter of clinical heart failure. The long-standing strains and resulting myocardial hypertrophy from chronic hypertension or valvular disease,[39,51] and the restriction of coronary flow from these or other causes may seriously deplete the efficiency of the pump.

Experimental injury to the normal heart in animals with intact circulation is no less interesting. It has seemed rather striking that the infliction of injury to *localized* areas of the heart muscle may not induce heart failure so frequently. Coelho and Rocheta[20] and Orias[100] ligated the coronary arteries of the exposed hearts of dogs; they noted only occasionally the occurrence of failure and pulmonary edema. Likewise, it is often possible to produce large infarcts in such heart preparations without evidence of functional breakdown.[48] In a number of experiments Roos and Smith[113] were able to ligate the three major coronary vessels of the hearts of dogs so that only small segments of intact muscle were visible. Ventricular fibrillation frequently occurred but heart failure was not observed. The remarkable experience of Starr, Jeffers and Meade[127] is noteworthy. They burned the right ventricles of dogs with a cautery so that large masses of the muscle were rendered necrotic. Despite such severe damage heart failure was not noted; no conspicuous rise in venous pressure occurred except terminally in some instances. In contrast to these studies, experimental myocardial damage tending to involve *all or most* of the normal heart muscle has seemed more consistently to provoke cardiac decompensation. The administration of chloroform or potassium chloride[52] or diphtheria toxin to dogs gives rise to some features of heart failure. However, cardiotoxins often exert deleterious effects on the peripheral vascular system so that the significance of dynamic changes may be difficult to judge in such experiments.

With the suggestion that generalized myocardial injury might significantly lower myocardial reserve and provoke failure, Roos and Smith[113] exposed the hearts of dogs with intact circulation and inflicted heart muscle injury by embolization of the coronary vessels with starch granules. They were able to demonstrate widespread damage to the cardiac tissue. Furthermore, they found that acute congestive heart failure resulted rather consistently from this form of tissue insult, manifested by marked ventricular dilatation, a fall in arterial pressure and peripheral venous engorgement with hepatic and pulmonary congestion.

In the light of these experimental suggestions it is possible that heart failure may be associated with myocardial changes which functionally incapacitate all or most of the muscle even though morphologic muscle change may be slight or absent. Localized myocardial death, unless superimposed on established disease processes or unless productive of ventricular fibrillation, appears to be less apt to provoke myocardial decompensation.

DYNAMICS OF MYOCARDIAL FAILURE

The fluid dynamics of the normal heart and circulation, and the changes wrought by failure of the heart, are complex and difficult to describe. Although many facts are at hand pertaining to this problem, the interpretation of these factual data is by no means agreed upon. For the purposes of this review, the more pertinent data will be presented briefly.

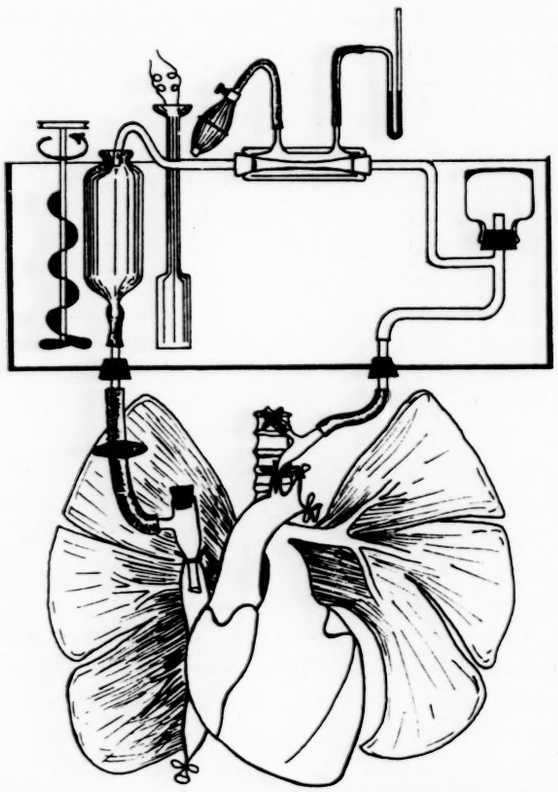


FIG. 1. Schematic diagram of the heart-lung preparation and heating unit as used in this laboratory. Venous reservoir and arterial connections of the preparation are enclosed in a constant temperature water bath. Note cannula tied into the superior vena cava which conducts blood from the venous reservoir to the right auricle. Arterial cannula is tied into the brachiocephalic artery which in the dog is the first branch of the aorta. The left subclavian artery and the aorta distal to it are securely ligated. The azygos vein and inferior vena cava are likewise tied off. Respiration is maintained by a Starling pump connected through an intratracheal cannula (not shown). A pinch clamp is usually applied to the venous tubing to regulate inflow and therefore output of the preparation. The peripheral resistance is secured by means of a section of Penrose tubing enclosed in a glass chamber; the tubing is compressed by air to any desired pressure. Such a preparation may be removed completely from the body of the dog but is usually left within the thoracic cage for mechanical stabilization.

Starling's Experiments with the Heart-Lung Preparation: The Law of the Heart. In 1914 Patterson and Starling[101] described the circulatory dynamics studied in the heart-lung preparation, amassing data from the wide experience of Starling and his pupils in the use of the preparation. (Fig. 1.) It should be recalled that the heart-lung preparation entails isolation of the cardiopulmonary circulation from the body, using an artificial peripheral resistance. A venous reservoir is connected to the right atrium for the inflow of blood to the heart. The heart and lungs are entirely denervated. The arrangement permits the individual control of the venous inflow (and cardiac output), "arterial" resistance and heart rate within certain limits. The information derived from these studies has been considered fundamental and has had great bearing on studies of cardiovascular function to the present. The essential points of these studies may be described as follows:

Patterson and Starling pointed out that the heart muscle is analogous to skeletal muscle in that following a contraction the muscle fibers must be lengthened by some stretching force before another effective contraction can occur. The lengthening force to the ventricular muscle is provided by the inflow of blood from the atria. Normally the pressure of inflow to accomplish distention may be very small. If, then, the venous inflow is cut off, the ventricles do not dilate in diastole and the heart beats for a time in emptiness. Oppositely, if venous inflow is in operation and ventricular diastole should become greatly prolonged, the inflowing blood will forcibly distend the ventricles to the maximum extent. In the regularly beating preparation the occurrence of the succeeding ventricular contraction prevents extreme distention of the chamber. Therefore, in the properly functioning heart-lung preparation, with moderate peripheral resistance (i.e., 100 mm. Hg) and regular rhythm, the rate and pressure of venous inflow may be ad-

justed to fill the ventricles during diastole without causing undue distention. Cardiac output then equals venous inflow. If due care is taken to keep the blood fresh, this circulatory load may be compatible with long periods of function.

Now if the venous inflow is further increased, greater tension will be exerted on the ventricular walls by the inflowing blood during diastole, and the ventricles fill and distend more rapidly before the following systole halts the process. The result is an increase in stroke output and, with constant heart rate, an increased minute volume flow from the heart. It is clear from these experiments that in the heart-lung preparation the cardiac output can be augmented by increased return of blood to the heart. Patterson and Starling found that this increased inflow to the heart, however, was attended by an elevation of venous pressure. Changes occur in this picture if the heart begins to tire. Assuming the inflow is sustained, as the force of systolic ejection diminishes residual blood will remain in the ventricles at the end of systole tending to hold up blood entering from the atria. The venous pressure then will rise and a greater distending force against the ventricles occurs, becoming more pronounced as the power of systolic contraction is gradually lost. Under these conditions the elevated venous pressure is associated with decreased cardiac output. A picture then emerges which seems analogous to the venous hypertension of clinical heart failure.

Patterson and Starling further indicated that other means besides the elevation of venous pressure operate to increase cardiac output. By heating or cooling the preparation to change the heart rate, they were able to show that with a given constant venous inflow, alteration of heart rate does not change the cardiac output per minute. Changes in heart rate affect individual stroke volumes but the net output per minute remains the same. Under these conditions a more rapid heart rate lowers the venous pressure. It is obvious that adjustments in the preparation may be made so that an increase in heart rate results in an *increase in cardiac output with the venous pressure remaining constant.* In order to do this a corresponding increase in venous inflow must be established.

The reports of Patterson and Starling are punctuated with the repeated observation that as a greater dilating force is applied to the ventricles they contract more vigorously. They point out a relationship between the diastolic volume and the energy output of the succeeding systole. This relationship was then described by Patterson, Piper and Starling[102] as "the law of the heart." They state: "The law of the heart is therefore the same as that of skeletal muscle, namely, that the mechanical energy set free on passage from the resting to the contracted state depends on the area of 'chemically active surfaces'; i.e., on the length of the muscle fibers."

Patterson and Starling made the circumspect statement that the dynamics of the heart-lung preparation are not strictly comparable to those in the intact animal and man. They were particularly concerned with the absence of negative intrapleural pressure effects in their experiments. In order to test negative pressure effect the hearts of heart-lung preparations were enclosed in cardiometers to which negative tension was applied. The results bore out the fact that readings in the venous manometers were reduced by the amount of the negative pressure used. Subsequently, Daly[24] enclosed heart-lung preparations in negative pressure chambers. He found that negative pressure expansion of the lungs produced a rise in cardiac output which he thought was due to the fall of resistance in the pulmonary vascular bed. Although the venous pressures were not reported in his paper, the trends indicate that ventricular filling was enhanced under negative pressure and that repercussions might be expected on the venous system in a lowering of venous pressure.

Measurement of Circulatory Flows and Pressures in Man. The perfection and utilization of the technic of right atrial catheterization

in man has broadened the horizons of study of cardiovascular physiology in normal persons and in those with heart disease. The essential features of the technic* need no introduction. In general, the method has proved of particular value in the

TABLE I
CARDIAC INDEX AND CARDIAC OUTPUT OF NORMAL HUMAN SUBJECTS

Author	Method Employed	Results
Cournand et al.[23]	Direct Fick	3.12 (2.12–4.01) (index)
Starr	Ethyl iodide	2.45 (index)
Nylin	Acetylene	2.46 (index)
Stead et al.[132]	Direct Fick	3.2 (2.6–3.9) (index)
Grollman[47]	Acetylene	2.2 (index)
McMichael et al.[89]	Direct Fick	5.3 L./min. (output)

recording of central venous, pulmonary arterial and right heart pressures. It has also provided a method of cardiac output determination when used in conjunction with the Fick principle[37] devised nearly eighty years ago. The Fick principle depends upon the calculation of the volume of blood passing through the lungs as determined by the uptake of oxygen and the rate of oxygen consumption. Details of the calculation will not be repeated here. The sampling of blood from the right atrial or ventricular cavity, made possible by the catheter method, provides a specimen of well mixed venous blood from all areas of the body. Although the cardiac output may be expressed in liter output per minute in individual cases, in order to unify the results relative to body size the output is frequently expressed as the minute volume output per square meter of body surface (i.e., cardiac index). Some workers[28,89] have preferred to describe cardiac output in relation to oxygen consumption per minute.

Normal values for cardiac output and cardiac index in man are compiled from the reports of several workers and are shown in Table I.

Although right heart catheterization and the Fick principle have been most widely utilized for cardiac output studies in recent years, it must be borne in mind that such

TABLE II
COMPARISON OF DIRECT FICK METHOD AND DYE METHOD IN ESTIMATING CARDIAC OUTPUT*

Patient	Direct Fick Method	Dye Method
Bronchiectasis, right pneumonectomy	4.7	5.5
Chronic emphysema, fibrosis	5.7	6.5
Normal	4.7	5.6
	10.1	13.6
Normal	7.1	9.6
	11.4	15.1
Normal	6.2	6.2
	8.2	8.4
Heart failure	4.1	3.1
Heart failure	5.7	5.6
Hypertension	6.2	5.0

* Compiled from the work of Hamilton et al.[50a] showing cardiac output in liters per minute.

figures of cardiac output should be interpreted as indicating only general trends of output. Individual values should be evaluated with caution. Hamilton and a large group of co-workers[50a] recently pointed out that the use of the dye method or the direct Fick procedure gave figures for cardiac output varying as much as 25 per cent in most instances. However, the results, with variable outputs, remained comparably similar. Therefore, employing either method, the trends of output become more reliable than do isolated values of output. There are errors and disadvantages in the use of either technic but it should be pointed out especially that the Fick principle, so widely used recently, is likewise vulnerable, for small differences in arteriovenous oxygen content may greatly magnify changes in the calculated cardiac output. (Table II.)

The effects on the dynamics of the heart and circulation of negative pressure, as shown by experiments on the heart-lung preparation, suggest that intrathoracic pres-

* For history and technical details of the method *cf.* references in Richards' paper.[112]

sure changes may exert important effects on cardiac performance in man. In this respect the contribution of Lauson and his associates[73] appears to be of importance. They studied the pressures in the right heart chambers, peripheral veins and systemic arteries in relation to various forms of respiration and in four instances with intrapleural pressure measurement. Their records show that during moderately deepened respiration a distinct pattern of pressure fluctuation is seen (both in the heart chambers and in the peripheral arteries) which are accentuated over the minimal fluctuations seen on quiet breathing. The tracings strikingly show that the fall of intra-auricular pressure associated with the onset of ventricular ejection is greater during inspiration than during expiration, due to the greater negativity of intrapleural pressure in the former. The difference in the pressure in the right atrium at the end of diastole and the pressure in the intrapleural space (the "net" auricular pressure) is increased in inhalation and lessens during exhalation. Similarly, the pressure in the right ventricle at the end of diastole and at the peak of the succeeding systole decreases during inspiration. At the height of inspiration these pressures, in relation to the negative intrapleural pressure (i.e., the "net" pressures), are increased just as in the case of the auricles. If the stroke volume of the right ventricle varies as a function of the *net* pressure of the filled ventricle at the end of diastole, an increase in stroke output of the right ventricle in inspiration occurs. Pressures in the femoral artery, recorded simultaneously, also indicate that left ventricular output waxes and wanes with expiration and inspiration, respectively. Lauson's group then brought forward evidence to show that these changes in right and left ventricular output, associated with respiration, are most probably due to changes in the resistance of the pulmonary vascular bed. In short, during inspiration more blood is held in abeyance in the lung and the left ventricular output decreases. In expiration, the opposite effects occur. The lungs, therefore, function as a sponge absorbing and then releasing fluid with changes in capacity of its vessels.

The net pressure fluctuations measured by right heart catheterization delineate the essential features of Starling's law of the heart in the case of the right ventricle: the greater the net pressure at the end of diastole, the greater is the net pressure developed at the peak of the following contraction.

Lauson et al. were able to demonstrate that exaggerated breathing and the performance of the Valsalva or Mueller maneuvers produced striking changes in right auricular tension. Marked rise in intrapleural pressure was associated with elevation of pressure in the auricular chamber while forcefully induced negative pressure produced striking depressions of auricular tension.

The importance of such data is evident and must receive further consideration as other factors are brought out concerning heart failure.

Cardiac Output in Myocardial Insufficiency. From the rather didactic demonstrations in the isolated heart with controlled circulation[101] one might expect that with a sustained venous return failure of the myocardium must be attended by a diminished systolic ventricular output. A reduction in cardiac output does, in fact, occur in many instances of heart failure reported in man.[53,55,91,111,134] However, frequently in cardiac insufficiency in man, output of the heart may be within normal range or even elevated above normal standards. Summarizing his data of output determination, Harrison[53] noted that: (1) the cardiac output may be normal, decreased or increased in patients with congestive heart failure; (2) the average range and values for cardiac output are similar in patients with heart disease whether actual failure is in progress or not; (3) in congestive disease with clinical improvement there may be an increased, diminished or normal output; (4) apparently normal individuals may have output figures as low as those in patients with heart failure. The acetylene method of

outflow determination, with its inherent faults, was used in obtaining these data.* The technic of right heart catheterization and the Fick principle has, in general, confirmed Harrison's observations. Stead and his co-workers[130,134] and Richards[112] have noted that in heart failure the cardiac output may be at normal standards, elevated or depressed. There is, nevertheless, a trend toward decreased cardiac output in cardiac insufficiency. Merrill[91] found a normal range of cardiac index of 2.3 to 4.1 (average 3.3) in healthy persons. In twenty-three cases of congestive heart disease the average cardiac index was below the normal mean in twenty cases. In ten of these latter cases the cardiac index was below 2.3 which is the lowest limit of the normal standard.

However, Stead et al.[134] and others have expressed uncertainty as to the reason for the lack of correlation between the state of heart failure and the resting cardiac output. A number of workers have made empirical suggestions as to factors influencing cardiac output during failure.[39,47,91] Stead, Warren and Brannon[134] studied two patients with severe anemia with congestive heart failure and two others in failure with thyrotoxicosis. These patients exhibited cardiac outputs that were considerably higher (cardiac indices of 4.5 or over) than is expected in persons of their size. These findings showed that congestive failure may develop in certain individuals before the resting cardiac output can fall to levels seen in normal subjects; this may be particularly true when thyrotoxicosis, anemia or other conditions are present to drive the cardiac output upward in response to the metabolic needs of the body. The suggestion is supported by the well known fact that anxiety[133] is one of the important causes of elevation of heart output in normal persons. Recently, augmented cardiac output has been noted in patients with thyrotoxicosis without circulatory insufficiency.[13] Brannon and his group[12] determined the cardiac output in eighteen patients with chronic anemia who did not have heart failure. In patients with hemoglobin values below 7 Gm. per cent and with hematocrits below 20 the cardiac output was usually elevated above resting output levels. In nine instances the hemoglobin was below 5 Gm. per cent and the average cardiac index was 6.5. Patients with moderate chronic anemia showed no significant changes in heart outflow. The results give added force to the suggestion that in a critical degree of anemia the blood requirements of the body are increased so that output and peripheral vascular flow[1] are elevated. If myocardial insufficiency develops, the cardiac output falls but it still may range within or above normal resting output.

In summary, the evidence indicates that heart failure occurs when the myocardium fails to deliver sufficient blood for body requirements, and the level of cardiac output may range from high to low (as against normal standards). The important consideration is that with cardiac failure the existing cardiac output, whatever its quantity, becomes *inadequate* to sustain normal body function.[130]

Effects of Heart Failure on Venous Pressure; Influence of Changes in Blood Volume and in Arterial Resistance. It will be recalled that in the controlled circulatory preparation[101] myocardial fatigue and failure of effective systolic ejection leads to increased residual ventricular blood at the end of systole. Inflow of blood to the heart is impeded and the venous pressure must rise. Dilatation of the heart occurs. Applied to the dynamics of the failing circulation in man this explanation for the elevation of venous tension seems simple and direct.[53,99]

The reconstruction of events in congestive heart failure leading to venous hypertension may be put as follows:[28,53] It is assumed that the right and left ventricles expel a given equal quantity of blood per stroke, but as a result of hypertension or other myocardial strain the stroke output of the left ventricle is reduced. Blood inflow to the left ventricle, however, remains unchanged; the left

* For methods of cardiac output previously employed refer to monographs of Grollman[47] and Harrison[53] and the paper of Hamilton.[50]

ventricle now receives more blood than it ejects. The pulmonary venous and left auricular tensions must then rise. The venous pressure changes in these chambers is probably largely dissipated because of their distensibility. The left ventricle, in order to accommodate the inflowing blood as well as the residual blood after the previous beat, now dilates and the greater diastolic stretch of the muscle fibers provokes stronger systolic contraction. The stroke volume is augmented. The cardiac output may then be restored to its original value but at the expense of increased diastolic size and elevated venous tension. These events may occur repeatedly and in varying degree, finally to include the right ventricle, auricle and peripheral venous system.[28]

Studies by Landis and his co-workers[68] indicate that changes in mechanics of circulation may lead to increase in venous pressure. They "exercised" normal, anesthetized dogs by electrical stimulation of the extremities. Such muscular activity evoked a tachycardia and a fall of venous pressure. When the myocardia of these dogs were damaged by interference with the coronary circulation, the venous tension did not rise during inactivity; however, when muscular movements were induced tachycardia occurred and venous pressure usually rose. In some experiments the venous pressure fell with muscular activity in dogs with damaged hearts but the fall was not so marked as in the animals with undamaged hearts. Unfortunately, these workers reported only very few experiments and none in which severe cardiac damage had been inflicted. Nevertheless, the evidence suggests that the picture of heart failure may be precipitated by physical activity when the "competence" of the heart muscle is impaired.

Observations on experimental heart failure were carried further by Roos and Smith.[113] They produced extensive generalized cardiac damage, and failure of the heart occurred which was sudden in onset and characterized by cardiac dilatation, elevation of intra-auricular tension and a decline in systemic arterial pressure. In experiments in which the blood volume was not increased by infusion, it was difficult to explain such abrupt changes in dynamics other than by the fundamental occurrence of cardiac dilatation and failure of effective systolic contraction. The dilatation then resulted in increased residual blood in the cardiac chambers in diastole, and entrance of blood from the venous system was then curtailed. It appeared to be failure of the heart to accept available blood from the veins that resulted in the increase of venous tension. Roos and Smith further showed that when the circulating blood volume was augmented by infusion, subsequent damage to the myocardium produced a more striking rise of venous pressure than was seen when the blood volume was not increased. In addition, quantitatively less myocardial injury was required to elevate the venous pressure and to produce cardiac dilatation and pulmonary congestion with the blood volume increased. It seems probable, therefore, that elevation of venous pressure is dependent further upon an abundant venous blood volume which is obstructed in its passage by incompetence of the heart muscle. The latter point finds further interesting support[113] in that severe myocardial injury frequently provokes shock, so that the bulk of blood becomes immobile in the peripheral vascular bed. Both the venous pressure and the systemic arterial pressures are low. Under these conditions the picture of cardiac failure does not develop.

The manifestations of myocardial failure in the experiments described resemble those usually described under the term "backward failure" in clinical cases: There appears to be curtailed stroke output of the damaged heart and a failure of the organ to move blood from a vastly overfilled venous system. The interesting and well known corollary to these observations is found in severe myocardial failure with intense venous engorgement and pulmonary edema (especially when acute in onset) in which the rapid removal of blood from the "available"

venous supply, by phlebotomy or application of tourniquets to the extremities,[27,58,63,74,141] may quickly permit recovery of the staggering heart muscle.[11,61] The induction of drastic diuresis by mercurial or other preparations[135] may likewise cause marked improvement in severe heart failure with venous distention, possibly through a similar mechanism.

A number of investigators[2,91,116,126,137] have been unable to accept as an adequate explanation the simple impounding of blood in the great veins for the rise in venous pressure in heart failure. Additional factors have been suggested. One consideration finding support in the opinions of several workers is the possibility of increased blood volume. Employing a dye technic, Gibson and Evans[44] noted in patients with heart disease that the blood volume increased as the severity of the heart failure increased. In these instances the hematocrit remained essentially unchanged, leading them to believe that cell volume and plasma volume increased proportionately. Meneely and Kaltreider[90] likewise evolved evidence suggesting a rise in blood volume in clinical heart failure. They were particularly struck by the high correlation between the degree of anoxemia and the increase in cell volume. The contention that hypervolemia occurs in patients with heart failure raises the important question of the possible effects on venous pressure and other manifestations of cardiovascular breakdown.

It may be re-stated here that the results of Roos and Smith[113] indicate that deterioration in cardiac function may be intensified when the blood volume is augmented by infusion before cardiac damage is produced. It is possible, then, that in chronic heart disease extending over a longer period of time any increase in blood volume will hasten the development of myocardial decompensation. The observations of Murphy, Correll and Grill[97] give indubitable evidence that augmentation of the circulating volume in cardiac patients by venous infusion may produce a marked rise of venous pressure with danger of overwhelming the diseased heart. In a group of interesting experiments Starr[126] found that the venous pressures of patients with congestive heart failure remained elevated after death. He could not account for the persistence of postmortem venous hypertension other than by excessive fluid content of the vascular system.

The mechanism of the increase in blood volume in congestive failure has been widely investigated. Particularly in recent years evidence has accumulated indicating that hypervolemia occurs with the retention of salt, and therefore of water, as a result of failure of renal elimination of salt. It has been shown in normal subjects that the administration of excessive amounts of salt will cause an increase in plasma volume, venous pressure and body weight.[46,84] In terms of heart failure, this circumstance may be accentuated. Warren and Stead[137] studied two patients in congestive heart failure, in each of whom compensation was restored by the use of digitalis, a salt-free regimen and diuretics. Thereafter, salt was added to the diets and digitalis therapy was continued. In subsequent days the plasma volume increased and the gain in weight shown by these patients rather paralleled the augmentation of blood volume. However, the venous pressure did not become elevated with the increase in blood volume and these workers were not disposed to agree that hypervolemia necessarily provokes an increase in venous tension although it may become elevated in due time. Furthermore, they reasoned that the salt retention by the kidneys may be a function of decreased cardiac output rather than of venous engorgement of the kidneys. Merrill's conclusion took similar lines.[91] He found a marked reduction in renal blood flow in cases of heart failure and noted that there was no significant correlation of venous pressure and renal flow in such cases. In addition, his evidence indicated that renal flow usually remained below 50 per cent of normal even though a reduction of venous pressure occurred. Merrill's study implied that sodium retention may result from a low glomerular fil-

tration rate secondary to decreased renal blood flow, for it was clearly demonstrated that inulin clearance (glomerular filtration) may be decreased from 33 to 50 per cent of normal in subjects with myocardial insufficiency. Assuming that tubular resorption is essentially normal in such subjects and that sodium filtration parallels that of inulin, reduced glomerular elimination of salt must occur. The consequent retention of sodium and of water then raises the blood volume, increasing cardiac load and enhancing the decline of the heart. Other studies[43,119] have confirmed the fact that marked sodium retention occurs in congestive heart disease and may be the dominant factor in the precipitation of peripheral edema; the studies imply intravascular and extravascular increase of fluid volume. Experiments by Reichsman and Grant[108] yielded contrasting results. They studied patients with chronic rheumatic heart disease in congestive heart failure. Compensation of the heart was secured by digitalis therapy. When digitalis was subsequently discontinued, the hearts failed again, resulting in a rise in venous pressure. The subjects gained weight and peripheral edema later appeared. The same authors[46] studied the effect of excessive salt administration in normal subjects. They noted an increase in blood volume and weight but only with an increased venous tension. The experiments therefore suggest that "backward failure" occurred in the cardiac subjects.

The studies of blood volume in relation to heart disease have been held in some question, principally because of the errors known to occur in the use of the T-1824 dye technic of volume determination.[104] The loss of dye into the extracellular tissue spaces or into the lymphatic system, and the escape of the substance into various blood depots constitute serious objections to the procedure. Nevertheless, the method has yielded basically uniform results in the hands of various workers.[28,44,90] Furthermore, Nylin and Hedlund[99a] employed a method of blood volume determination using erythrocytes tagged with radioactive phosphorus. They were able to reaffirm the occurrence of an increased blood volume in patients with failing hearts. The latter method confirmed the results of others employing the T-1824 method. Inherent faults in blood volume determinations are present but the tendency toward an increased blood volume in congestive failure seems amply established.

Although the blood volume has been considered of primary importance in heart failure, it has been suggested also that redistribution of blood within the vascular bed by vasoconstriction may influence the venous pressure.[4,38] It has been noted clinically that the systemic blood pressure may be normal during periods of decreased cardiac output. However, that the blood pressure may reach high levels during heart failure is a matter of common knowledge to physicians. The pathogenesis of vasoconstriction in congestive failure is not clearly understood and, to date, the phenomenon has not been well reproduced under controlled, experimental conditions. Landis and his co-workers[68] maintained that vasoconstriction may be a compensatory reaction to venous engorgement. Other evidence[91] has been advanced that vasoconstriction occurs in consequence of diminution of cardiac output. The direct importance of vasoconstriction in influencing the picture of heart failure is thus uncertain; however, it is possible that if the blood pressure is sufficiently elevated, not only is the direct load on the myocardium further increased but there may be inhibition of any trend toward shock. Pooling of peripheral blood is prevented and a greater quantity of blood may be impounded in the venous system.[113]

Hypothesis of Backward and Forward Failure. Controversies concerning the mechanism of heart failure have chiefly centered about the train of events occurring in the wake of myocardial dilatation and diminution in cardiac output. An impressive body of evidence has been cited to support the view that curtailment of cardiac function may

diminish the acceptance of blood from the venous system by the heart. A rise of venous pressure then ensues if blood returns to the venous system from the peripheral bed at a greater rate than its passage into the heart ("backward failure"). As the blood volume later becomes increased, by decreased renal blood flow and possibly by a factor of renal engorgement, venous tension may be enhanced and peripheral edema occurs.[46,84,108] This view has been challenged by those who consider that decreased cardiac output and consequent decreased renal blood flow, salt retention and increased blood volume are the first important events occurring in heart failure ("forward failure"). A rise of venous pressure, therefore, may not result from incompetence of heart action but follows when hypervolemia becomes established. These conflicts of views may be presented briefly. Stead and Warren[133] suggested that in patients with normal blood volume the level of venous pressure is not important in determining variations in cardiac output. In a wide variety of conditions a normal differential in pressure between the atrium and ventricle appeared to be adequate to maintain considerable increases in stroke volume.[138] On this basis, the suggestion was made that the Starling principle may not be applicable to cardiovascular dynamics in man in most instances. However, in subjects with low blood volume an increase in venous pressure was noted to accompany a rise of cardiac output. Furthermore, Stead and Warren[133] have stated that in patients with arteriovenous fistulas temporary interruption of the abnormal vascular communication results in an immediate drop in cardiac output. However, the right atrial pressure remains unchanged. They concluded that means other than venous pressure changes must be investigated to explain alteration in stroke volume in man.

The conclusions of Stead and Warren were criticized by Roos and Smith[113] largely on the basis of errors that may arise on technical grounds. Since the work of Lauson et al.[73] indicated net right ventricular and auricular pressures are widely varied in respiration, the intra-auricular tension with respect to intrapleural pressure may not coincide with the actually recorded atrial pressure. Therefore it appears possible that the "effective" right auricular tension could have been elevated in the instances described. Furthermore, it may be pointed out[113] that pitfalls may lie in the use of the intracardiac catheter, for a water manometer attached to the catheter tube may record auricular pressure only during inspiration. A corresponding rise of tension in expiration may not occur. A significant discrepancy between "effective" and apparent atrial tensions may thus arise from this technical factor. It is further apparent that the observation of an elevation of cardiac output without an increase in venous pressure does not invalidate the Starling principles. Recalling studies with the heart-lung preparation[101] if the heart rate is increased, venous inflow and cardiac stroke output may be augmented without a rise of venous pressure. The indication is clear that in conditions in man in which heart rate is increased, an elevation of cardiac output may be achieved without a rise of venous pressure.

In this connection it is of interest that Cohen et al.[22] found that cardiac output to be elevated in a number of patients with arteriovenous fistula. When the fistulas were closed temporarily, a decrease in cardiac output occurred together with a deceleration of heart rate. There was a concomitant fall in right atrial pressure. When the arteriovenous shunts were re-opened, the cardiac output and heart rate quickly rose; the right atrial tension likewise showed a small increase. The changes in auricular pressure were not of large magnitude, although the trend was consistent. These authors considered the variations in cardiac output in their subjects to be largely dependent on changes in heart rate rather than upon the altered levels of venous tension. Their findings are in general accord with the Starling principles in that altered rates of inflow to and output from the hearts were

accomplished with only small resultant changes in venous tension.

The experimental and clinical evidence at present is of insufficient scope to explain completely the mechanisms by which cardiac output is altered under normal and pathological conditions and the events contingent upon myocardial breakdown. The balance of evidence rather suggests that the phenomena of "backward failure" may be dominant in a given instance as heart failure begins, but the factors of "forward failure," including salt and fluid retention, become no less important as congestive failure progresses.

CONSEQUENCES OF HEART FAILURE

Pulmonary Edema. Of the vicissitudes to which the cardiac patient is subject, none is more dramatic than the occurrence of massive pulmonary edema. The condition has long been considered a manifestation of left ventricular failure.[83] Indeed this clinical impression was strengthened by early attempts to produce pulmonary edema experimentally. Many years ago Welch[142] noted the occurrence of pulmonary edema resulting from ventricular overload following aortic constriction. Following this lead, other workers[21] brought forth evidence to suggest that critical interference with function of the left ventricle may lead to massive edema of the lungs. The belief prevailed among these workers that edema of the lungs resulted directly from the intense congestion induced by myocardial failure. Furthermore, experiments in which the pulmonary veins or left auricle were constricted[21,77,93,117] also induced pulmonary edema in some experiments. On the other hand Sahli[117] and others[55,77,93] were unable to confirm the contention that pulmonary edema resulted from drastic curtailment of left ventricular function. Other experimental evidence has been evolved to indicate that injury to the right ventricular muscle may likewise lead to acute and intense pulmonary edema.[18] It is of further interest that acute pulmonary edema in patients with mitral stenosis is less common[83] although it is the condition *par excellence* in which pulmonary venous drainage is expected to be impaired. The clinical and experimental evidence at hand, therefore, provides no certain clue as to the mechanism of acute pulmonary edema from failure of the myocardium. Pulmonary congestion alone does not appear to be the precipitating cause and other mechanisms must be investigated.

Diseases of the central and peripheral nervous systems may be complicated by pulmonary edema in the absence of demonstrable heart disease. Injuries of the head causing fracture of the skull, cerebral hemorrhage and tumor or infection of the brain[83,140] may be complicated by a high incidence of lung edema. There is likewise ample experimental evidence to indicate that injury to nerves may produce pulmonary edema,[35,36,121] such as stimulation of the stellate ganglia or of other structures of the vegetative nervous system.[35,55,83,121] The frequent development of the condition following epinephrine administration in rabbits is well known.[59,82] In the latter experiments the seizure can be controlled by central nervous system depressants such as morphine, papaverine and chloretone[82,83] and aggravated by the stimulants metrazol and caffeine. These effects of the central nervous system on the vascular structure of the lungs are poorly understood. Many studies have shown that pulmonary circulation is under neurogenic control,[25,26,54] and the possibility that "neurogenic" pulmonary edema is a result of excessive vasodilatation or diminished vasoconstriction has been strongly suggested by such studies. Furthermore, the possibility that nerve impulses may alter capillary permeability has been advanced and such a mechanism must be considered.[31] Whether neurogenic edema is in any way related to the pulmonary edema of heart failure is uncertain at present.

The appearance of pulmonary edema following exposure to gaseous and parenteral toxins[55] has raised the possibility of a toxic mechanism in the pathogenesis of lung edema from heart disease. The frequent occurrence of spontaneous edema in the

heart-lung preparation appears to be due to a toxic agent, for it may result from the use of stored blood[67] or whipped blood.[98] In addition, the high protein content of the edema fluid indicates capillary damage, possibly toxic.[95] It has further been suggested that the lung edema frequently occurring in shock is due to the action of an "H-substance" carried to the lungs from the site of injury.[96]

While there is doubt as to the primary agents in the production of pulmonary edema in man, the role played by secondary factors is more certain. The liability of the lung to edema because lymphatic drainage is "bottlenecked" by the anatomic limitations of the lymphatic system must be considered.[30] The ease of spread of fluid through the lung because of the absence of a true alveolar membrane and the many pores in the alveolar walls have been demonstrated.[76] The dependence of lung tissue upon alveolar air for oxygen makes it unusually susceptible to a rapidly spreading edema. As fluid accumulates in the lung it spreads easily and in so doing removes more lung tissue from its oxygen supply. The capillaries are rendered more permeable and accelerated filtration of fluid from the vessels into the airspace of the lung occurs.[30]

Hepatic Congestion. Swelling and tenderness of the liver are frequent signs of a failing heart. The congestion of the central veins with hemorrhage, loss of central parenchymal cells, fibrosis and fat deposition are well known features of the "nutmeg" liver.[75] These changes have been ascribed to the high venous pressure of right heart failure.[39] On the other hand, the mechanical effect of venous congestion may not seem to offer a wholly adequate explanation for the central lesions. The direction of flow from the peripheral to the central hepatic veins indicates that the pressure in the peripheral veins must be the higher, yet the cells in the peripheral portion of the lobules are preserved. Furthermore, under the conditions of congestion the central veins are no more dilated than those about the lobular periphery. Other explanations for central hepatic lesions have been advanced. Rich[109,110] expressed the opinion that anoxemia resulting from venous stasis may produce such lesions. The location of the lesion and the occurrence of similar pathologic changes in anemia support the possibility.[110] Mallory[86] proposed that central hepatic lesions result from toxemia or infectious processes. Nevertheless, it is possible to produce lesions closely resembling those of chronic passive congestion of the liver by obstructing the inferior vena cava and hepatic veins in experimental animals.[8,147] Neither infection nor toxemia appear to be prerequisites. Although the lesion of central congestion, atrophy and fibrosis is almost wholly confined to cases of heart failure, other hepatic lesions have been noted. Katzin et al.[62] reported 286 autopsied cases with chronic passive congestion of the liver. Of these forty-eight showed biliary or diffuse fibrosis of the liver.

The estimation of the frequency of true "cardiac cirrhosis" has been complicated by the multiplicity of definitions of the term. If "cardiac cirrhosis" is used to mean hepatic fibrosis in congestive failure, the condition is not rare; it may occur in 50 per cent of cardiacs who have been in failure for a period of nine months or more.[62] If, however, the term refers to an atrophic, fibrosed liver with ascites and splenomegaly, the condition is uncommon.[75]

Liver function is also disturbed in cardiac failure. Latent jaundice is frequently present, with serum bilirubin levels ranging from 0.5 mg. to 8 mg. per cent. Bromsulfalein excretion tests often show excessive retention with return to normal on compensation of the heart.[5,7,75]

The pathogenesis of latent jaundice in heart failure is debatable. That there is an extrahepatic factor of excessive bilirubin formation seems quite certain. The elevation of stool and urine urobilinogen can be explained only on such a basis,[109] and the discovery of hemosiderin deposits in many organs is further evidence of extrahepatic jaundice.[40] The importance of the role of the liver is more uncertain. However, low

bilirubin tolerance[75] and the pathologic lesions in the liver suggest a definite hepatic influence although the severity of the lesions is often not in proportion to the degree of bilirubinemia.[62]

Frank jaundice is uncommon in cardiac decompensation[17,60,75] but its occurrence is considered an ill omen. That there is an additional factor to cause a transition from the latent jaundice of chronic passive congestion to frank clinical jaundice has been strongly suggested.[75] Pulmonary infarction frequently precedes the onset of jaundice. In one series studied by Kugel and Lichtman[75] 94 per cent of cardiac patients with clinical jaundice had pulmonary infarction. The hemolysis of red blood cells in the hemorrhagic lung infarct has been considered the source of the added bilirubin producing the jaundice.[75] Others have disagreed with this point of view.[110] Whatever the mechanism of jaundice in these cases may be it is apparent that pulmonary infarction is the most frequent precipitating agent in cardiac jaundice.

Ascites occurs in 82 to 88 per cent of cardiac patients with heart failure, 15 per cent of whom require paracentesis.[75] The mechanism of its production is unknown; its occurrence suggests a true cirrhosis.[75] Other factors in the accumulation of ascites may be a low plasma protein and concentration of an antidiuretic substance. The urine of cirrhotic patients contains large amounts of an unmetabolized antidiuretic substance similar to the posterior pituitary principle.[106] The liver in heart failure may have a similar metabolic defect and the presence of such a substance may contribute to the formation of ascitic fluid and edema.

Edema. The pathogenesis of cardiac edema has been the object of much study and controversy. Many reviews of the subject have been written[28] and an extensive examination of the subject at this time would be repetitious.

The factors postulated by Starling[25] in the production of edema have been carefully analyzed and their importance in cardiac edema investigated. The evidence indicates that of the theoretic factors productive of edema (increased capillary hydrostatic pressure, increased tissue osmotic pressure, decreased plasma osmotic pressure, decreased tissue tension or increased capillary permeability) only an increased capillary hydrostatic pressure seems to be of primary importance in the production of cardiac edema. Diminished plasma osmotic pressure due to hypoproteinemia does occur in many cardiacs[56,103,115,120] but when present is of slight degree and is apparently not in itself sufficient to cause edema formation.[2] Increased capillary permeability due to anoxemia or dilatation[65] has been considered a possible factor[3,70] and therapy with 45 per cent oxygen has been known to produce improvement and diuresis in patients.[3] But the low protein content of cardiac edema fluid[10,128,137] is strong evidence that there is no important capillary permeability increase, and an increase in permeability due to dilatation has been shown not to occur.[71] Also, the frequent absence of edema in congenital cardiacs and in emphysematous patients who have severe anoxemia[33,137] suggests that the degree of anoxemia seen in congestive heart failure does not in itself produce edema. In view of the low protein content of cardiac edema fluid an increase in tissue osmotic pressure can hardly be an important factor. In addition, there is no evidence that diminution in tissue tension is an important primary factor although in patients whose tissues have been previously distended by edema fluid the recurrence of edema may be facilitated. Lymphatic obstruction secondary to the rise in venous pressure has been considered a possible factor in formation of edema and has been found to be present,[88] yet the high protein content of lymphedema fluid[28] is quite unlike that of cardiac edema and doubt is cast on the importance of lymphatic obstruction in the pathogenesis of cardiac edema.

An excessive retention of salt and water by the kidney is known to occur in heart failure[14,16,43,92,107] and has been considered

a primary factor in edema formation. The evidence indicates that there are two possible factors of dominant importance in the production of cardiac edema: an increase in capillary hydrostatic pressure and a retention of salt and water. Interpretation of the evidence concerning these disturbances has resulted in the postulation of two theories. According to the first, failure of the heart results in a rise in venous pressure which is reflected in a rise in capillary pressure[72] which in turn causes increased filtration from the capillary extravascular fluid accumulation and reduction in circulating blood volume. Salt and water are retained by the kidney in an effort to restore blood volume.[104] Experimental and clinical evidence has shown that the rise in venous pressure is present in many cardiac patients,[6,44,55,111] may be present in all under certain conditions and is reflected in a rise of capillary pressure.[72] Such a pressure rise produced experimentally leads to the accumulation of edema fluid[64] similar in composition to that of cardiac edema fluid.[69,103] The other theory emphasizes the salt and water retention, probably resulting from the diminution in cardiac output known to occur in many if not all patients in heart failure. Such retention increases blood volume and in so doing increases capillary hydrostatic pressure and filtration from the capillary. The rise in venous pressure is considered a secondary factor. The debate has not been reconciled.

Although many of the controversies in studies of the various phenomena of cardiac failure have been irreconcilable and confusing, the questions raised by such differences of opinion have stimulated further investigation of these problems. It is in re-study of controversial questions that the hope of greater knowledge lies.

SUMMARY

The mechanisms of cardiac failure are discussed as (1) injury of the myocardium leading to heart failure, (2) the dynamics of heart failure and (3) consequences of myocardial decompensation.

1. Myocardial injury may be judged frequently by morphologic changes in the hearts of persons who have died with heart failure. It is pointed out that the causes of functional breakdown of the heart are obscure but evidence suggests that generalized myocardial damage may be of prime importance in compromising cardiac function.

2. Studies by Starling and his pupils on the heart-lung preparation suggested certain principles of cardiodynamic function, some of which have been invoked to explain cardiodynamic changes in man. The more recent studies of cardiocirculatory problems in man, especially those utilizing the technic of right heart catheterization, are reviewed. The possible roles of cardiac output, increased blood volume and venous hypertension in the dynamics of heart failure are presented.

3. The pathologic physiology of pulmonary edema, hepatic congestion and peripheral edema in consequence of heart failure is briefly reviewed. The available evidence indicates that pulmonary edema may not result from simple congestion of lung tissue but that other factors, at present obscure, may operate in congested lungs to produce edema. Characteristic hepatic lesions and impairment of liver function may occur from congestive heart failure. The possible mechanisms of functional impairment, certain liver function tests and the occurrence of jaundice and ascites in heart failure are particularly discussed.

The authors are indebted to Dr. W. B. Wood, Jr., Department of Medicine, for many helpful criticisms in the preparation of this review.

REFERENCES

1. Abrams, D. I., Fierst, S. M. and Flachs, N. Resting peripheral blood flow in the anemic state. *Am. Heart J.*, 25: 609, 1943.
2. Altschule, M. D. The pathological physiology of chronic cardiac decompensation. *Medicine*, 17: 75, 1938.
3. Barach, A. L. and Richards, D. W., Jr. Effects of treatment with oxygen in cardiac failure. *Arch. Int. Med.*, 48: 325, 1931.
4. Bazett, H. C. Blood volume and cardiovascular adjustments. *Am. Heart J.*, 21: 423, 1941.

5. Bernstein, M., Le Winn, E. B. and Simkins, S. Heart disease and liver function. *J. Lab. & Clin. Med.*, 28: 1, 1942.
6. Bloomfield, R. A. Lauson, H. D., Cournand, A., Breed, E. S. and Richards, D. W. Recording of right heart pressure in normal subjects and in patients with chronic pulmonary disease and various types of cardiovascular disease. *J. Clin. Investigation*, 25: 239, 1946.
7. Blumberg, N. and Schloss, E. M. Effect of circulatory factors on bromsulfalein excretion in liver disease. *Am. J. M. Sc.*, 213: 470, 1947.
8. Bolton, C. Pathological changes in the liver resulting from passive congestion experimentally produced. *J. Path. & Bact.*, 19: 258, 1914.
9. Bolton, C. The pathology of cardiac dropsy. *Brit. M. J.*, 1: 642, 1917.
10. Bramkamp, R. G. Protein content of subcutaneous edema fluid in heart disease. *J. Clin. Investigation*, 14: 34, 1935.
11. Brams, W. A. and Katz, L. N. Studies on the overdistended heart. I. Effects of venesection. *Am. J. Physiol.*, 98: 556, 1931.
12. Brannon, E. S., Merrill, A. J., Warren, J. V. and Stead, E. A. The cardiac output in patients with chronic anemia as measured by the technique of right atrial catheterization. *J. Clin. Investigation*, 24: 332, 1945.
13. Brannon, E. S., Stead, E. A. and Warren, J. V. The cardiac output in thyroid disase. Quoted by Stead and Warren. *Arch. Int. Med.*, 80: 237, 1947.
14. Bridges, W. C. Low sodium diet and free fluid intake in the treatment of congestive heart failure. *New England J. Med.*, 234: 573, 1946.
15. Budelman, G. and Kara-Eneff, S. Ueber das Verhalten des Muskeltonus beim Aderlass. *Klin. Wchnschr.*, 19: 1103, 1940.
16. Burch, G. E. Disturbances of water and salt balance in congestive heart failure. *Mod. Concepts Cardiovas. Dis.*, 17: 1948.
17. Cantarow, A. Studies of hepatic function. *Arch. Int. Med.*, 56: 521, 1935.
18. Cataldi, G. M. Oedème aigu du poumon dans les lésions expérimentales du ventricle droit. *Arch. d. mal. du coeur*, 28: 604, 1935.
19. Coelho, E. and Ribiero, M. Étude expérimentale sur deux formes pathogéniques de l'oedème aigu du poumon: mécanique et toxique. *Arch. d. mal. du coeur*, 29: 383, 1936.
20. Coelho, E. and Rocheta, J. Récherches électrocardiographiques sur la ligature des artères coronaires chez le chien. *Compt. rend. Soc. de biol.*, 102: 203, 1929.
21. Coelho, E. and Rocheta, J. Études expérimentales sur la pathogénie de l'oedème aigu du poumon. *Ann. méd.*, 34: 91, 1933.
22. Cohen, S. M., Edholm, E. G., Howarth, S., McMichael, J. and Sharpey-Schafer, E. P. Cardiac output and peripheral blood flow in arteriovenous fistula. *Clin. Sc.*, 7: 35, 1948.
23. Cournand, A., Riley, R. L., Breed, E. S., Baldwin, E. and Richards, D. W. Measurement of cardiac output in man using the technique of catheterization of the right auricle or ventricle. *J. Clin. Investigation*, 24: 106, 1945.
24. Daly, I. deB. The resistance in the pulmonary vascular bed. *J. Physiol.*, 69: 238, 1930.
25. Daly, I. deB. Physiology of the bronchial vascular system. *Harvey Lect.*, 31: 235, 1936.
26. Daly, I. deB. Sensory receptors in the pulmonary vascular bed. *J. Exper. Physiol.*, 27: 123, 1937.
27. Danzer, C. S. The pathogenesis and treatment of dyspnea in the light of recent experiments. *Ann. Int. Med.*, 2: 239, 1928.
28. Davis, J. O. and Smith, J. R. Pathogenesis of peripheral cardiac edema. *Am. J. Med.*, 3: 704, 1947.
29. Drinker, C. K., Peabody, F. W. and Blumgart, H. L. Effect of pulmonary congestion on ventilation of the lungs. *J. Exper. Med.*, 33: 77, 1922.
30. Drinker, C. K. Pulmonary Edema and Inflammation. Cambridge, 1945. Harvard Press.
31. Engel, D. Influence of the sympathetic nervous system on capillary permeability. *J. Physiol.*, 99: 161, 1940–41.
32. Evans, C. L. and Matsuoka, Y. The effect of various mechanical conditions on the gaseous metabolism and efficiency of the mammalian heart. *J. Physiol.*, 49: 378, 1915.
33. Fahr, G. and Erschler, I. Studies of factors concerned in edema formation; hydrostatic pressure in capillaries during edema formation in right heart failure. *Ann. Int. Med.*, 15: 798, 1941.
34. Fahr, G. and Buehler, M. S. A physiologic definition of acute congestive heart muscle failure. *Am. Heart J.*, 25: 211, 1943.
35. Farber, S. Pulmonary edema: vagotomy in the rabbit. *J. Exper. Med.*, 66: 297, 1937.
36. Farber, S. Studies on pulmonary edema: the pathogenesis of neuropathic pulmonary edema. *J. Exper. Med.*, 66: 405, 1937.
37. Fick, A. Ueber die Messung des Blutquantums in den Herzventrikeln. *Sitzungsb. d. phys.-med. Gesellsch. zu Wurzburg*, 1870.
38. Fineberg, M. H. and Wiggers, C. J. Compensation and failure of the right ventricle. *Am. Heart J.*, 11: 255, 1936.
39. Fishberg, A. M. Heart Failure. Philadelphia, 1940. Lea & Febiger.
40. Fishberg, A. M. Jaundice in myocardial insufficiency. *J. A. M. A.*, 80: 1516, 1923.
41. Fishberg, A. M., Hitzig, W. M. and King, F. H. Circulatory dynamics of myocardial infarction. *Arch. Int. Med.*, 54: 997, 1934.
42. Friedman, B., Clark, E. G., Resnik, H. and Harrison, T. R. Effect of digitalis on the cardiac output of persons with congestive heart failure. *Arch. Int. Med.*, 56: 710, 1935.
43. Futcher, P. and Schroeder, H. A. Studies on congestive heart failure. II. Impaired renal excretion of sodium chloride. *Am. J. M. Sc.*, 204: 52, 1942.
44. Gibson, J. G. and Evans, W. A., Jr. Clinical studies of blood volume. III. Changes in blood volume, venous pressure and blood velocity rates in chronic congestive heart failure. *J. Clin. Investigation*, 16: 851, 1937.
45. Gollwitzer-Meier, Kl. and Krueger, E. Herzenergetik und Strophanthinwirkung bei verschiedenen Formen der experimentellen Herzinsuffizienz. *Arch. f. d. ges. Physiol.*, 238: 251, 1936–37.

46. Grant, H. and Reichsman, F. The effects of ingestion of large amounts of sodium chloride on the arterial and venous pressures of normal subjects. *Am. Heart J.*, 32: 704, 1946.
47. Grollman, A. The Cardiac Output of Man in Health and Disease. Springfield, Ill., 1932. Charles C. Thomas.
48. Gross, L., Mendlowitz, M. and Schauer, G. Hemodynamic studies in experimental coronary occlusion. I. Open chest experiments. *Am. Heart J.*, 13: 647, 1937.
49. Grossman, M. Weitere experimentelle Beiträge zur Lehre von der Lungenschwellung und Lungenstarrheit. *Ztschr. f. klin. Med.*, 20: 397, 1892.
50. Hamilton, W. F. Notes on the development of the physiology of cardiac output. *Federation Proc.*, 4: 183, 1944.
50*a*. Hamilton, W. F., Riley, R. L., Attayh, A. M., Cournand, A., Fowell, D. M., Himmelstein, A., Noble, R. P., Remington, J. W., Richards, D. W., Wheeler, N. C. and Witham, A. C. Comparison of the Fick and dye methods of measuring cardiac output. *Am. J. Physiol.*, 153: 309, 1948.
51. Harrison, T. R., Ashman, R. and Larson, R. M. Congestive heart failure. *Arch. Int. Med.*, 49: 151, 1932.
52. Harrison, T. R., Friedman, B. and Resnik, H. Mechanism of acute experimental heart failure. *Arch. Int. Med.*, 57: 927, 1936.
53. Harrison, T. R. Failure of the Circulation. Baltimore, 1939. Williams & Wilkins.
54. Hebb, C. O. Bronchomotor responses. *J. Physiol.*, 99: 67, 1940.
55. Henneman, P. H. Acute pulmonary edema. *New England J. Med.*, 235: 590, 619, 1946.
56. Hermann, G. R. Blood plasma proteins in patients with heart failure. *Ann. Int. Med.*, 24: 893, 1946.
57. Heyer, H. E. and Harrison, T. R. Backward failure theory of congestive heart disease. *Mod. Concepts Cardiovas. Dis.*, 16, 1948.
58. Howarth, S., McMichael, J. and Sharpey-Schafer, E. P. Effects of venesection in low output heart failure. *Clin. Sc.*, 6: 41, 1946.
59. Johnson, S. Experimental production and prevention of acute edema of the lungs in rabbits. *Proc. Soc. Exper. Biol. & Med.*, 25: 181, 1927–1928.
60. Jolliffe, N. Liver function in congestive heart failure. *J. Clin. Investigation*, 8: 419, 1929–1930.
61. Katz, L. N. and Brams, W. A. Studies on the overdistended heart. II. The rôle of relaxation in filling the distended and overdistended heart. *Am. J. Physiol.*, 98: 569, 1931.
62. Katzin, H. M., Waller, J. V. and Blumgart, H. L. Cardiac cirrhosis of the liver. *Arch. Int. Med.*, 64: 457, 1939.
63. Kountz, W. B., Smith, J. R. and Wright, S. T. Observations on the effect of tourniquets on acute cardiac crises, normal subjects, and chronic heart failure. *Am. Heart J.*, 23: 624, 1942.
64. Krogh, A., Landis, E. M. and Turner, A. H. Movement of fluid through human capillary wall in relation to venous pressure and to colloid osmotic pressure of the blood. *J. Clin. Investigation*, 11: 61, 1932.
65. Krogh, A. Anatomy and Physiology of Capillaries. New Haven, 1922. Yale Univ. Press.
66. Kutschera-Aichbergen, H. Ueber Herzschwäche. *Wien. Arch. f. inn. Med.*, 18: 209, 1929.
67. Lambert, R. K. and Gremels, H. On the factors concerned in the production of pulmonary edema. *J. Physiol.*, 61: 98, 1926.
68. Landis, E. M., Brown, E., Fauteaux, M. and Wise, C. Central venous pressure in relation to cardiac "competence," blood volume, and exercise. *J. Clin. Investigation*, 25: 237, 1946.
69. Landis, E. M., Jonas, L., Angevine, M. and Erb, W. Passage of fluid and protein through the human capillary wall during venous congestion. *J. Clin. Investigation*, 11: 713, 1932.
70. Landis, E. M. Micro-injection studies of capillary permeability. VIII. Effect of oxygen lack on permeability of capillary wall to fluid and plasma proteins. *Am. J. Physiol.*, 83: 528, 1928.
71. Landis, E. M. Micro-injection studies of capillary permeability. *Am. J. Physiol.*, 81: 124, 1927.
72. Landis, E. M. Micro-injection studies of capillary blood pressure in human skin. *Heart*, 15: 209, 1929–1930.
73. Lauson, H. D., Bloomfield, R. A. and Cournand, A. The influence of the respiration on the circulation in man. *Am. J. Med.*, 1: 315, 1946.
74. Lemierre, A. and Bernard, E. Récherches sur les indications et sur l'action physiologique de la saignée. *Presse méd.*, 34: 704, 1926.
75. Lichtman, S. S. Diseases of the Liver, Gallbladder, and Bile Ducts. Philadelphia, 1942. Lea & Febiger.
76. Loosli, C. C. Interalveolar communications in the lung. *Arch. Path.*, 24: 743, 1937.
77. Lowit, M. Ueber die Entstehung des Lungenoedems. Ein Beitrag zur Lehre von Lungenkreislauf. *Beitr. path. Anat. u. allg. Path.*, 14: 401, 1893.
78. Lubarsch, O. Pathologische Morphologie und Physiologie des Ödems. *Zentralbl. f. Herz-u. Gefässkrankh.*, 4: 344, 1912.
79. Luisada, A. A. and Sarnoff, S. J. Paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors. *Am. Heart J.*, 31: 270, 1946.
80. Luisada, A. A. and Sarnoff, S. J. Paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors. II. Mechanical and neurogenic elements. *Am. Heart J.*, 31: 282, 1946.
81. Luisada, A. A. and Sarnoff, S. J. Paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors. III. Pharmocologic experiments. *Am. Heart J.*, 31: 293, 1946.
82. Luisada, A. A. Beitrag sur Pathogenese und Therapie des Lungenödems und des Asthma Cardiale *Arch. f. exper. Path. u. Pharmakol.*, 132: 313, 1928.
83. Luisada, A. A. Pathogenesis of pulmonary edema. *Medicine*, 19: 475, 1940.
84. Lyons, R. H., Jacobsen, S. D. and Avery, N. L. Increase in the plasma volume following the administration of sodium salts. *Am. J. M. Sc.*, 208: 148, 1944.
85. Mack, I., Grossman, M. and Katz, L. N. The effect of pulmonary vascular congestion on the distensibility of the lungs. *Am. J. Physiol.*, 150: 654, 1947.

86. Mallory, F. B. Chronic passive congestion of the liver. *J. M. Research*, 24: 455, 1911.
87. McGuire, J., Shore, R., Hanenstein, V. and Goldman, F. Relation of cardiac output to congestive heart failure. *Arch. Int. Med.*, 63: 290, 1939.
88. McMaster, P. D. Lymphatics and lymph flow in the edematous skin of human beings with cardiac and renal disease. *J. Exper. Med.*, 65: 373, 1937.
89. McMichael, J. and Sharpey-Schafer, E. P. Cardiac output in man by a direct Fick method. *Brit. Heart J.*, 6: 33, 1944.
90. Meneely, G. R. and Kaltreider, N. L. A study of the volume of blood in congestive heart failure. Relation to other measurements in fifteen patients. *J. Clin. Investigation*, 22: 521, 1943.
91. Merrill, A. J. Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of forward failure as the primary cause of edema. *J. Clin. Investigation*, 25: 389, 1946.
92. Merrill, A. J. Mechanism of salt excretion in congestive heart failure. *Proc. Am. Federation Clin. Research*, 2: 8, 1946.
93. Modrakowski, G. Beobachtungen an der überlebenden Säugetierlunge. II Mitteilung. Uber die experimentelle Erzeugung von Lungenödem. *Arch. ges. Physiol.*, 158: 527, 1914.
94. Moe, G. K. and Visscher, M. B. The mechanism of failure in the completely isolated mammalian heart. *Am. J. Physiol.*, 125: 461, 1939.
95. Moon, V. H. Experimental pulmonary edema. *Arch. Path.*, 21: 565, 1936.
96. Moon, V. H. Shock mechanisms and pathology. *Arch. Path.*, 24: 642, 794, 1937.
97. Murphy, F. D., Correll, H. and Grill, J. C. The effects of intravenous solutions on patients with and without cardiovascular defects. *J. A. M. A.*, 116: 104, 1941.
98. Newton, W. H. Pulmonary edema in the cat heart-lung preparation. *J. Physiol.*, 75: 288, 1932.
99. Nylin, G. On the amount of, and changes in, the residual blood of the heart. *Am. Heart J.*, 25: 598, 1943.
99*a*. Nylin, G. and Hedlund, S. Weight of the red blood corpuscles in heart failure determined with labelled erythrocytes during and after decompensation. *Am. Heart J.*, 33: 770, 1947.
100. Orias, O. The dynamic changes in the ventricles following ligation of the ramus descendens anterior. *Am. J. Physiol.*, 100: 629, 1932.
101. Patterson, S. W. and Starling, E. H. On the mechanical factors which determine the output of the ventricles. *J. Physiol.*, 48: 357, 1914.
102. Patterson, S. W., Piper, H. and Starling, E. H. The regulation of the heart beat. *J. Physiol.*, 48: 465, 1914.
103. Payne, S. A. and Peters, J. P. Plasma proteins in relation to blood hydration. VIII. Serum proteins in heart disease. *J. Clin. Investigation*, 11: 103, 1932.
104. Peters, J. P. Role of sodium in the production of edema. *New England J. Med.*, 239: 353, 1948.
105. Peters, H. C. and Visscher, M. B. The energy metabolism of the heart in failure and the influence of drugs upon it. *Am. Heart J.*, 11: 273, 1936.
106. Ralli, E. P., Rabson, J. S., Clarke, D. and Hoagland, C. L. Factors influencing ascites in patients with cirrhosis of the liver. *J. Clin. Investigation*, 24: 316, 1945.
107. Reaser, P. B. and Burch, G. E. Radiosodium studies in congestive heart failure. *Proc. Soc. Exper. Biol. & Med.*, 63: 543, 1946.
108. Reischman, F. and Grant, H. Some observations on the pathogenesis of edema in cardiac failure. *Am. Heart J.* 32: 438, 1946.
109. Rich, A. R. Pathogenesis of forms of jaundice. *Bull. Johns Hopkins Hosp.*, 47: 338, 1930.
110. Rich, A. R. and Resnick, W. H. On the mechanism of jaundice following pulmonary infarction in patients with heart failure. *Bull. Johns Hopkins Hosp.*, 38: 75, 1926.
111. Richards D. W. Jr., Cournand A. Darling, R. C., Gillespie, W. H. and Baldwin, E. Pressure of the blood in the right auricle, in animals and man: under normal conditions and in right heart failure. *Am. J. Physiol.*, 136: 115, 1942.
112. Richards, D. W., Jr. Contributions of right heart catheterization in the physiology of congestive heart failure. *Am. J. Med.*, 3: 434, 1947.
113. Roos, A. and Smith, J. R. The production of experimental heart failure in dogs with intact circulation. *Am. J. Physiol.*, 153: 558, 1948.
114. Rössler, R. Ueber experimentelle Herzschädigung durch Koronargefässverengerung und ihre Beeinflussung durch Pharmaka. *Arch. f. exber. Path. u. Pharmakol.*, 153: 1, 1930.
115. Rowe, A. H. Refractometric studies of serum proteins in nephritis, cardiac decompensation, diabetes, anemia and other chronic diseases. *Arch. Int. Med.*, 19: 354, 1917.
116. Ryder, H. W., Molle, W. E. and Ferris, E. B. The influence of the collapsibility of veins on venous pressure, including a new procedure for measuring tissue tension. *J. Clin. Investigation*, 23: 333, 1944.
117. Sahli, H. Zur Pathologie und Therapie des Lungenödems. *Arch. f. exper. Path. u. Pharmakol.*, 19: 433, 1885.
118. Schlomka, G. Commotio cordis and ihre Folgen. Die Einwirkung stumpfer Brustwandtraumen auf des Herz. *Ergebn. inn. Med. u. Kinderheilk.*, 47: 1, 1934.
119. Schroeder, H. A. Studies on congestive heart failure. I. The importance of restriction of salt as compared to water. *Am. Heart J.*, 22: 153, 1941.
120. Seymour, W. B., Pritchard, W. H., Langley, L. P. and Hayman, J. M. Cardiac output, blood and interstitial fluid volume, total circulating serum protein and kidney function during cardiac failure and after improvement. *J. Clin. Investigation*, 21: 229, 1942.
121. Short, R. H. D. Pulmonary changes in rabbits after bilateral vagotomy. *J. Path. & Bact.*, 56: 355, 1944.
122. Smith, J. R. and Jensen, J. Observations on the effect of theophylline aminoisobutanol in experimental heart failure. *J. Lab. & Clin. Med.*, 31: 850, 1946.
123. Socin, C. Experimentelle Untersuchungen über

akute Herzschwäche. *Arch. ges. Physiol.*, 160: 132, 1914–1915.

124. STARLING, E. H. and VISSCHER, M. B. The regulation of the energy output of the heart. *J. Physiol.*, 62: 243, 1927.
125. STARLING, E. H. Physiological factors involved in causation of dropsy. *Lancet*, 1: 1267, 1896.
126. STARR, I. Role of the "static blood pressure" in abnormal increments of venous pressure. II. Clinical and experimental studies. *Am. J. M. Sc.*, 199: 40, 1940.
127. STARR, I., JEFFERS, W. A. and MEADE, R. H. The absence of conspicuous increments of venous pressure after severe damage to the right ventricle of the dog, with a discussion of the relation between clinical congestive failure and heart disease. *Am. Heart J.*, 26: 291, 1943.
128. STEAD, E. A. and WARREN, J. V. Protein content of extracellular fluid in normal subjects after venous congestion and in patients with cardiac failure, anoxemia and fever. *J. Clin. Investigation*, 23: 283, 1944.
129. STEAD, E. A., WARREN, J. V. and BRANNON, E. S. Cardiac output in congestive heart failure. *Am. Heart J.*, 35: 529, 1948.
130. STEAD, E. A. Relation of cardiac output to symptoms and signs of congestive heart failure. *Mod. Concepts Cardiovas. Dis.*, 16: 1948.
131. STEAD, E. A. and EBERT, R. V. Shock syndrome produced by failure of the heart. *Arch. Int. Med.*, 69: 369, 1942.
132. STEAD, E. A., WARREN, J. V., MERRILL, A. J. and BRANNON, E. S. The cardiac output in male subjects as measured by the technique of right atrial catheterization. *J. Clin. Investigation*, 24: 326, 1945.
133. STEAD, E. A. and WARREN, J. V. Cardiac output in man. *Arch. Int. Med.*, 80: 237, 1947.
134. STEAD, E. A., WARREN, J. V. and BRANNON, E. S. Cardiac output in congestive heart failure. An analysis of the reasons for the lack of correlation between the symptoms of heart failure and the resting cardiac output. *Am. Heart J.*, 35: 529, 1948.
135. STEINBERG, F. U. and JENSEN, J. The effect of theophylline aminoisobutanol on the circulation in congestive heart failure. *J. Lab. & Clin. Med.*, 31: 857, 1946.
136. VISSCHER, M. B. The restriction of the coronary flow as a general factor in heart failure. *J. A. M. A.*, 113: 987, 1939.
137. WARREN, J. V. and STEAD, E. A., JR. Fluid dynamics in chronic congestive heart failure. *Arch. Int. Med.*, 73: 138, 1944.
138. WARREN, J. V., BRANNON, E. S., STEAD, E. A., JR. and MERRILL, A. J. The effect of venesection and the pooling of blood in the extremities on the arterial pressure and cardiac output in normal subjects with observations on acute circulatory collapse in three instances. *J. Clin. Investigation*, 24: 337, 1945.
139. WARREN, J. V., STEAD, E. A., JR. and BRANNON, E. S. The cardiac output in man. A study of some of the errors in the method of right heart catheterization. *Am. J. Physiol.*, 145: 458, 1946.
140. WEISMAN, S. S. Edema and congestion of the lungs from intracranial hemorrhage. *Surgery*, 6: 722, 1939.
141. WEISS, S. and ROBB, G. P. Treatment of cardiac asthma (paroxysmal cardiac dyspnea). *M. Clin. North America*, 16: 961, 1933.
142. WELCH, W. H. Zur Pathologie des Lungenödems. *Virchows Arch. f. path. Anat.*, 72: 375, 1878.
143. WHITE, H. L. Measurement of cardiac output by a continuously recording conductivity method. *Am. J. Physiol.*, 151: 45, 1947.
144. WINSOR, T. and BURCH, G. E. Use of the phlebomanometer: normal venous pressure values and a study of certain clinical aspects of venous hypertension in man. *Am. Heart J.*, 31: 387, 1946.
145. WITT, D. B., LINDNER, E. and KATZ, L. N. The dynamic effect of acute experimental poisoning of the heart with diphtheria toxin. *Am. Heart J.*, 13: 693, 1937.
146. YEOMANS, A., PORTER, R. R. and SWANK, L. Observations on certain manifestations of circulatory congestion produced in dogs by rapid infusion. *J. Clin. Investigation*, 22: 33, 1943.
147. ZIMMERMAN, A. M. and HILLSMAN, J. A. Chronic passive congestive of the liver. *Arch. Path.*, 9: 1154, 1930.

Combined Staff Clinics

Cholesterol Metabolism and Arteriosclerosis

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. DAVID SEEGAL: This clinic is concerned with an examination of the possible role of a disordered cholesterol metabolism in the pathogenesis of atherosclerosis and arteriosclerosis. This problem has engaged many investigators and has led to considerable controversy. We shall limit ourselves to a small segment of the field. For more general and complete discussions you might consult the reviews of Cowdry,[1] Duff,[2] Winternitz,[3] Hueper[4] and a recent Biological Symposium.[5] These reports contain excellent presentations of current hypotheses concerning the causation of atherosclerosis, including mechanical factors, cholesterol, arterial vascularization and colloid imbalance.

Atherosclerosis is characterized by the deposition of lipid substances in the intima. We consider atherosclerosis to be an early manifestation of arteriosclerosis. Both the early and late stages of arteriosclerosis may be present without symptoms. With progressive vascular damage, signs of illness usually appear because of an inadequate flow of blood through the coronary, cerebral or peripheral arteries.

The medical and socio-economic importance of arteriosclerosis requires no emphasis in this clinic. It is disappointing, however, that so little is known about its cause, natural history, treatment or prevention. Yet arteriosclerosis is probably responsible for more disability and death than any other single cause of disease.

Among the reasons for this slow development in our knowledge is that present methods for the diagnosis of arteriosclerosis are not much improved over those available thirty years ago. We still make the diagnosis of arteriosclerosis on the basis of such presumptive evidence as old age, or *post hoc* when organic impairment has been produced by occlusive arterial disease. Even after an individual is subjected to complete study we have great difficulty determining the presence, distribution and severity of arteriosclerosis. We are often confused in trying to discriminate between the relative preponderance of intimal and medial sclerosis, which are quite different pathologic entities. These limitations are increased by what Dr. Wolbach described as the "vagaries" of arteriosclerosis—the disparity in the extent of the process in some vessels as compared with others in the same individual. Furthermore, it is not unusual to observe early and advanced lesions of arteriosclerosis side by side in the same aorta. The differences in age of contiguous plaques would suggest that the causative agent acts discontinuously.

Our fallibility in the diagnosis of arteriosclerosis is more clearly shown when we carry out the orderly sequences of history and physical examination. The reports of Musser, White and Boas have called attention to the importance of information

[1] COWDRY, E. V. Arteriosclerosis: A Survey of the Problem. New York, 1933. McMillan.

[2] DUFF, L. Experimental cholesterol arteriosclerosis and its relationship to human arteriosclerosis. *Arch. Path.*, 20: 81–123, 257–304, 1935.

[3] WINTERNITZ, M. C. The Biology of Arteriosclerosis. Springfield, Ill., 1938. C. C. Thomas.

[4] HUEPER, W. C. Arteriosclerosis: a general review. *Arch. Path.*, 38: 162–181, 245–285, 350–364, 1944; 39: 51–65, 117–131, 187–216, 1945.

[5] Biological Symposia. Vol. XI. Aging and Degenerative Diseases. Lancaster, Pa., 1945. J. Cattell Press.

concerning the family history in special instances of arteriosclerosis. More detailed data are required in this category. In the past and present history a well documented episode of myocardial infarction is good evidence for the presence of arteriosclerosis. Similarly, clinical patterns associated with occlusion of the arteries to the brain or lower extremities yield useful information in the diagnosis of arteriosclerosis.

The physical examination may be helpful or misleading. The wide pulse pressures in elderly individuals without overt aortic insufficiency reflect the relative inelasticity of the long tubes beyond the aortic arch. Retinal study may show arteriosclerotic changes but this finding does not necessarily indicate the presence or degree of this disease in other vessels. Severe arteriosclerosis of the coronary arteries is found frequently in individuals whose eyeground examination is reported normal. Too often thickened or even beaded radial arteries lead to the diagnosis of general arteriosclerosis. In the great majority of these cases the abnormality in the radial artery is the result of medial (Mönckeberg) and not intimal sclerosis. When a diagnosis is obscure, the general appearance and the age of a patient often leads to the presumptive diagnosis of "general arteriosclerosis" as the chief cause of a patient's disability. Dr. K. B. Turner and I found "general arteriosclerosis" one of the most frequent erroneous diagnoses in the medical clinicopathology records of this hospital between 1917 and 1935.

Certain x-ray methods are rewarding in the diagnosis of arteriosclerosis. Isolated calcified plaques are sometimes visualized in various portions of the aorta. Calcified rings may be demonstrated in the aortic valve area by the technic of Sosman. Medial arterial calcification is seen in x-rays of the extremities and intimal sclerosis may be detected by using contrast media. Calcified areas in the renal, mesenteric and cerebral arteries may be seen from time to time. However, x-rays are of little service in the detection of coronary arteriosclerosis.

There are no chemical tests for arteriosclerosis.

We are forced to conclude that we lack methods to diagnose and quantitate the degree of arteriosclerosis in man.

Nor do the data now available, whether experimental or clinical, afford a sound basis for the treatment of arteriosclerosis. Work indicating that diets low in certain foodstuffs might diminish or reverse arteriosclerosis is suggestive but too new to be evaluated.

Before considering the evidence bearing on the relation of cholesterol to arteriosclerosis, I have asked Dr. Bevans to describe the pathologic sequences in arteriosclerosis. She will show that arteriosclerosis is not an inevitable concomitant of aging. She will further comment on the vagaries of arteriosclerosis and on the disparity in age of contiguous lesions in the aorta.

Dr. Margaret Bevans: Before describing the development of arteriosclerotic lesions in man I should like to call attention to two anatomic changes which normally occur in the arteries: First, the intima of the aorta increases from a single layer of endothelial cells in the newborn to a well defined fibrous layer lined by endothelium in the adult. Secondly, the elastic tissue in the wall of all arteries deteriorates progressively throughout the life span. The consequent stretching is apparent to all of us who have followed the evolution of our own temporal arteries. This is *not* arteriosclerosis.

For purposes of this discussion, we shall consider atherosclerosis as an early stage of arteriosclerosis, being fully aware that this is a controversial point. The earliest lesion which pathologists can recognize is the deposition of lipoid material beneath the endothelium of the intima. Even at this early stage the lipoid is found there in star-shaped connective tissue cells, extracellularly in the tissue spaces and in macrophages which have a foamy cytoplasm. Dissolution of some of the macrophages occurs and cholesterol and fatty acid crystals are found in the layers of the intima. The adjacent fibrous tissue undergoes a

FIG. 1. Human arteriosclerosis; section of aorta showing moderately advanced intimal arteriosclerosis. A fibrous tissue layer covers the foamy cells giving a white appearance to the plaque in the gross specimen; hematoxylin and eosin stain, × 163.

FIG. 2. Human arteriosclerosis, advanced lesion; the intimal plaque is composed of a dense layer of fibrous tissue; thrombus is seen on the surface. Deep in the plaque calcium has been deposited and the media is compressed beneath the plaque; hematoxylin and eosin stain, × 20.

degenerative change characterized by breaking up of the fibrillar strands into a granular substance. Proliferation of the superficial intimal fibrous tissue results in thickening of the intima above the deposit. (Fig. 1.) This process is reflected by the yellow streaks and the white and yellow raised plaques on the intimal surface, the white areas being those with the thicker layer of overlying fibrous tissue. Up to this point the alteration can be considered atherosclerosis. Changes subsequent to the formation of the atheromatous plaques are various and unpredictable. They are all grouped under the heading of arteriosclerotic lesions but before I describe them I should like to emphasize three facts: (1) There is a gradual merging of these changes with the atheromatous stage described previously. (2) Almost invariably all of these changes can be found in the same artery. (3) To the best of my knowledge no relation of lesions to intervals of time has been established.

The deeper layers of the atheromatous plaques undergo necrosis and calcium is deposited in these areas. (Fig. 2.) Eventually the entire plaque and the overlying intima may be converted into a mass of calcium. More often the increased rigidity due to calcium within the plaque causes stretching and injury to the superficial intima layers sufficient to produce ulceration. Necrosis of the deeper layers of the atheromatous plaque may spread upward before calcification occurs. When this happens the superficial layers of the intima ulcerate and a mass of soft atheromatous material is swept into the blood stream leaving a rough base in which many anisotropic cholesterol crystals may be identified. With the interruption of the endothelial lining of the intima the familiar sequelae of thrombus formation and organization ensue. Intramural hemorrhages about the atheromatous and sclerotic plaques must also be mentioned. These cause further damage to the vascular wall.

Since this type of arteriosclerosis is essentially a disease of the intima, we shall not discuss changes in the media except to say that they occur secondary to changes in the intima.

We have no explanation to offer for the vagaries of distribution of arteriosclerosis. Some workers have believed that strain on the thinner areas where branching occurs plays a part in the localization of sclerotic plaques but this is not invariably the observed distribution. Others have suggested that increased blood pressure plays an important part in the development of the plaques, citing as examples the occurrence

FIG. 3. Human aorta with severe arteriosclerosis illustrating the progressive nature of the disease. Small yellow plaques representing the earliest lesions lie close to old ulcerated plaques.

of pulmonary artery sclerosis principally in the presence of pulmonary hypertension and the severe generalized arteriosclerosis that is often the companion of systemic hypertension.

It has long been recognized by pathologists that arteriosclerosis bears no absolute relation to age though its incidence certainly increases with the years. We are accustomed to seeing aortas and coronary arteries almost entirely free of sclerosis in elderly people. We also find advanced sclerosis in individuals before the fourth decade of life. The recent review of the Army Medical Museum material by Yater indicates the frequency of diffuse coronary artery disease in persons below the age of forty, the necropsy material comprising over 400 men with diffuse coronary sclerosis. In this series individuals with a familial history of hypertension were four times as frequent as those without such a background.

Is arteriosclerosis a continuously progressive disease? Side by side in most sclerotic vessels there are early atheromatous plaques and old calcified ulcerated lesions. (Fig. 3.) This suggests that arteriosclerosis is a reaction to discontinuous stimuli which may occur at any time in the life of an individual.

In summary, the earliest detectable lesions of human arteriosclerosis are deposits of lipoid in the intima. Necrosis, calcification and ulceration of atheromatous material in the initial deposit follow in undetermined periods of time. The reasons for the localization of plaques are not altogether clear. Arteriosclerosis bears no absolute relation to age and seems to be a discontinuous disease process.

DR. SEEGAL: We shall now consider the evidence relating arteriosclerosis to cholesterol metabolism. There are three chief reasons for the interest of investigators in such a relation. In the first place, cholesterol and its esters occur in considerable amounts in arteriosclerotic plaques. Secondly, it has been possible to produce arteriosclerosis by feeding excess cholesterol to rabbits, guinea pigs and chickens; moreover, Dr. Steiner and Dr. Kendall have found that lesions closely resembling those seen in human arteriosclerosis develop in the dog following the ingestion of cholesterol and thiouracil over a prolonged period. Finally, it is a common clinical experience that arteriosclerosis develops prematurely and with great severity in such diseases as uncontrolled diabetes mellitus and chronic glomerulonephritis. Hypercholesterolemia is common in these conditions.

Dr. Batchelor will review some of the pertinent facts regarding cholesterol metabolism.

DR. WILLIAM H. BATCHELOR: Cholesterol, like the bile acids, sex hormones, hormones

of the adrenal cortex and pro-vitamin D, is a sterol, one of a group of polycyclic compounds found in all plant and animal tissues, "neutral and comparatively stable substances which occur partly in the free condition and partly esterified with higher fatty acids."[6] Cholesterol is quantitatively the most important sterol of animal tissues. "It is present in all cells of the animal organism, in largest amounts in the brain and nerve tissue, in the suprarenal glands, and in egg yolk. The solid matter of the human brain contains as much as 17% of the substance."[6]

Relevant to our discussion today is the finding of Schoenheimer and others that cholesterol constitutes 40 to 65 per cent of the phospholipid-free fats extracted from arteriosclerotic lesions of human aortas. Moreover, and this may prove to be of special interest as regards arteriosclerosis, Ruzicka and his co-workers were able to identify at least four oxidation products of cholesterol in the lipids obtained from arteriosclerotic human aortas, namely, $\Delta^{3,5}$ cholestadiene-7-one, $\Delta^{4,6}$ cholestadiene-3-one, 7-β hydroxycholesterol and 3,5,6 cholestantriol. (Fig. 4.) The presence of these compounds suggests the possibility of oxidative metabolism of cholesterol in the body. The physiologic significance of some of these substances is now under investigation by Dr. Kendall and his co-workers.

In addition to these oxidation products of cholesterol, a reduction product, the saturated compound dihydrocholesterol, has been found in small amounts in the sterols isolated from various organs (Schoenheimer).

The cholesterol of the diet can be absorbed in the small intestines. In cholesterol feeding experiments the ease with which it is absorbed depends upon its physical state. In finely divided form or in solution in fats, it is readily absorbed; fed in crystalline form it is largely excreted unchanged.

In man about 0.5 Gm. of cholesterol is secreted into the intestines each day in the bile. This is probably largely reabsorbed. The major part of the sterols excreted in the feces are the reduction products of cholesterol designated coprosterol and dihydrocholesterol. These reduced sterols are not reabsorbed to any important degree. The mechanism of their reduction is not clear. It has been suggested that it is the result of the action of bacterial flora of the large intestines. Since reduction of cholestrol *in vitro* does not yield coprosterol, a direct reduction of cholesterol seems unlikely. Experiments on both dog and man indicate that cholestenone is an intermediate in the biochemical conversion of cholesterol to coprosterol.

Cholesterol clearly is not an essential dietary constituent. Human subjects and experimental animals maintained on cholesterol-free diets not only show relatively constant serum cholesterol levels but continue to excrete sterols in the feces. This indicates synthesis of cholesterol in the body, a process which Schoenheimer was able to demonstrate by careful balance studies in the rat.

There has been a great deal of speculation as to the precursors of cholesterol and its rate of synthesis in the body. Earlier theories postulated the direct formation of cholesterol from fatty acids and several schemes for this conversion were proposed but no adequate proof has been advanced for the formation of sterols directly from fatty acids. Plant sterols differ but slightly from cholesterol in their structure but they are not absorbed in the alimentary tract of animals.

Actually no real progress was made in elucidating the metabolism of cholesterol until the introduction of isotope technics, notably by Schoenheimer, Rittenberg and Bloch. If a constant concentration of heavy water is maintained in the body fluids of an animal, all synthetic reactions take place in a medium of D_2O and all compounds synthesized will contain deuterium. From a study of the uptake of heavy hydrogen it is possible to measure the rate of synthesis of the compound even if nothing is known of the actual chemical mechanism. Schoen-

[6] Fieser, L. F. Chemistry of Natural Products Related to Phenanthrene. 2nd ed., pp. 111, 112. New York, 1937. Reinhold Pub. Corp.

heimer and Rittenberg made such rate studies with mice on a cholesterol-free diet. By sacrificing mice after different intervals, it was found that the deuterium content of the body cholesterol steadily increased until a maximum value was reached. From analysis of the results it was calculated that half of the body cholesterol was destroyed and resynthesized in approximately thirty days. About 2 per cent of the cholesterol was replaced every day. Similar studies by Waelsch and Sperry showed that the cho-

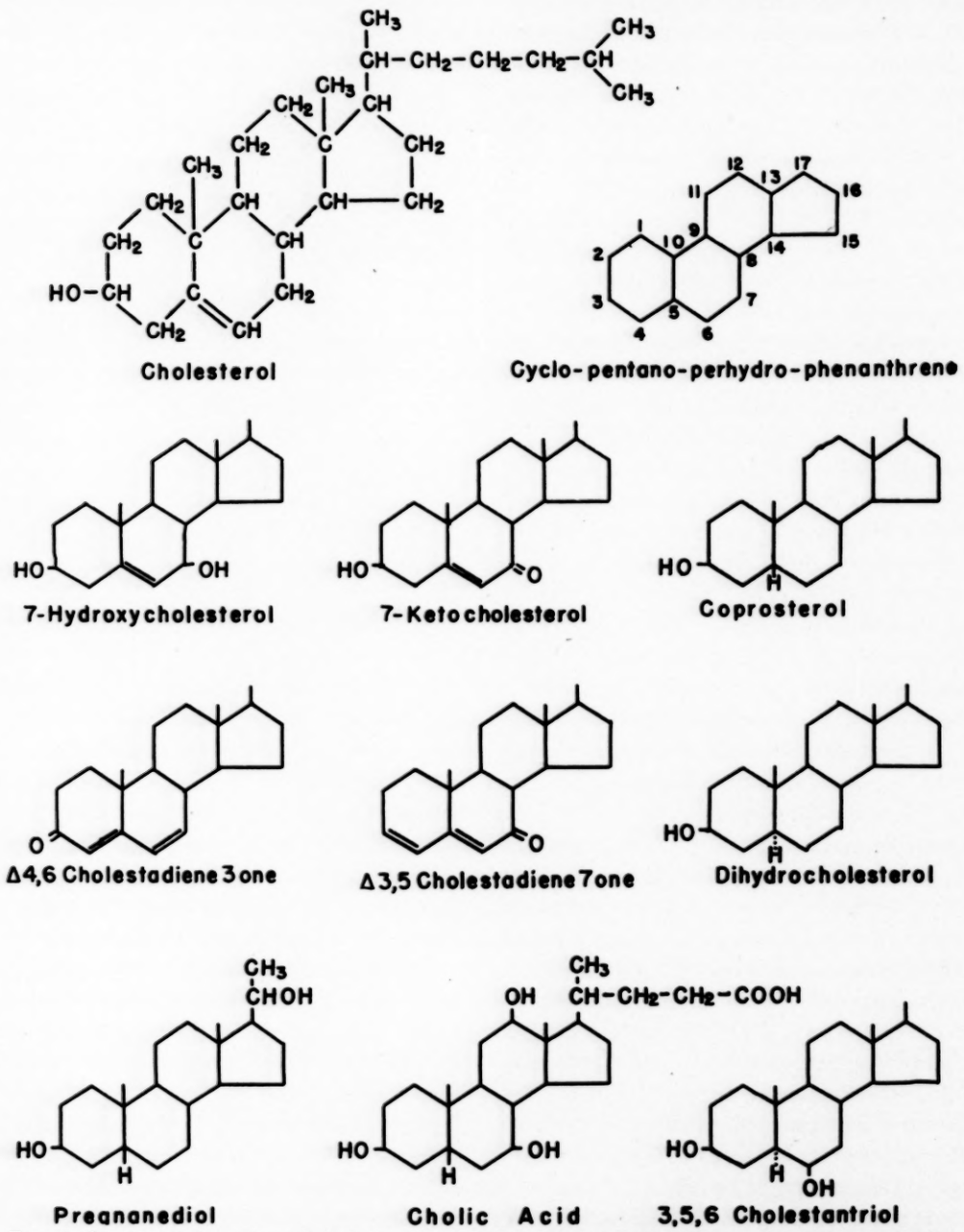


FIG. 4. Structural formulas of cholesterol and related compounds. The cyclopentano-perhydrophenanthrene nucleus is common to all these compounds with the positions numbered as indicated. In all compounds the substituent groups at C_{10}, C_{13} and C_{17} are the same as in cholesterol unless otherwise indicated. Where C_5 is fully reduced, two stereoisomers arise and are differentiated by solid and broken lines. Erratum: The H attached to C_5 in the formula 3,5,6 cholestantriol should be an OH.

lesterol in the brain of adult mice differs from cholesterol elsewhere in that it is not replaced by newly synthesized cholesterol during the course of the experiment.

Schoenheimer and Rittenberg showed that after the mice have been on experiment for a long time the deuterium concentration in the cholesterol becomes equal to half that of the body water. This demonstrates that during the synthesis half of the hydrogen atoms of the compound are derived from water. A reasonable deduction is that cholesterol must be built up from compounds of low molecular weight. A search by the isotope technic finally revealed one precursor of cholesterol. Bloch and Rittenberg found that feeding of deuterio-acetate to rats results in the formation of deuterio-cholesterol. Acetate therefore is a precursor of cholesterol; but since acetate is not an important dietary component, it in turn must be synthesized. The major sources of acetate are the fatty acids and the ketogenic amino acids. However, since carbohydrates are readily converted into fats in the body, any dietary component may possibly act as a precursor of cholesterol. Bloch[7] has recently reviewed current views as to the sources of acetic acid in the body and its general importance as a source of carbon atoms in the synthesis of larger molecules.

Bloch, Borek and Rittenberg studied the site of synthesis of cholesterol in the body by incubating tissue slices from different organs with heavy water, with deuterio-acetate, and with acetate containing deuterium in the methyl group and C^{13} in the carbonyl group. Synthesis of cholesterol could be demonstrated only in the liver slices. The rate of synthesis by the liver slices was high enough to warrant the deduction that cholesterol is formed principally in the liver. Recently, however, Chaikoff and co-workers made the interesting observation that adrenal cortical tissue also is capable of synthesis of cholesterol from acetate *in vitro*.

Little is known about the breakdown of cholesterol in the body. It has been supposed that the ring system of the molecule is comparatively stable. However, now that it has been shown that the molecule can be built up from small molecules, we cannot eliminate the possibility that the ring system may also be degraded.

Isotope studies have shown that cholesterol is the mother substance of at least two related steroids. Suspensions of deuterio-cholesterol were injected into dogs. After collecting the bile over a three-day period the dogs were sacrificed and the organs analysed. Deuterio-cholic acid was isolated from the bile. The quantitative data indicated that most if not all of the cholic acid was derived from cholesterol. Analysis of the organs showed that the largest amount of the injected cholesterol had been deposited in the lungs and the liver. None was detected in the brain or spinal cord. The feeding of deuterio-cholesterol to a pregnant woman resulted in the excretion of deuterio-pregnandiol. This compound while not a sex hormone is generally believed to be a reduction product of the sex hormone progesterone. At present it is not possible to say whether or not other sex hormones are derived from cholesterol.

Additional studies of this kind are needed to clarify our understanding of cholesterol metabolism and its possible relation to arteriosclerosis. The work already reported has made it clear that controlling cholesterol intake may have very little effect upon the over-all cholesterol metabolism since the body can synthesize cholesterol from protein, fats and carbohydrates.

Dr. David Rittenberg: Dr. Batchelor has reviewed our present knowledge of this subject very well. I should like to point out, however, that the experiments with deuterio-acetate account for less than half the carbon atoms in cholesterol. It appears therefore that other precursors must be involved. We have recently obtained evidence that administration of labeled acetone results in the formation of labeled cholesterol. This reaction occurs not only in the intact animal but also in surviving liver

[7] Bloch, K. The metabolism of acetic acid in animal tissues. *Physiol. Rev.*, 27: 594, 1945.

tissue. It is possible that acetone is the precursor of the methyl groups in the sterol.

DR. SEEGAL: With this background we might now turn to a closer examination of the problem of arteriosclerosis itself. For reasons already indicated it is difficult to attack the problem directly in man. Such progress as has been made stems largely from animal experiment. I have asked Dr. Kendall to review this field, with special reference to the work of his own group.

DR. FORREST E. KENDALL: Dr. Seegal has stressed the fact that arteriosclerosis cannot be adequately diagnosed and followed in man. Clinical investigation in this field has consisted largely of the collection of laboratory data in the hope that some relationship might be found between these data and a subsequent demonstration of arteriosclerosis. Since the disease process extends over a period of years and even decades and since exact information of what has taken place can be obtained only at the end of the process, clinical progress has necessarily been slow. Many attempts have therefore been made to reproduce and study the disease in experimental animals. Intimal lesions resembling those seen in man have been produced experimentally in the rabbit, chicken and dog by greatly increasing the serum cholesterol level.

In the rabbit intimal arteriosclerosis almost never occurs spontaneously but, as Anitschkow showed in 1913, addition of cholesterol to the diet of the rabbit results in the production of intimal arterial lesions. The extent of the lesions and the length of time required to produce them depend upon the degree of hypercholesterolemia. Anitschkow in 1932 reviewed the work up to that time and presented arguments for considering that the rabbit lesions are identical with those of human arteriosclerosis. However, Duff[2] and other investigators pointed out that: (1) The distribution of the lesions in rabbits is different from that seen in man in that the thoracic aorta and pulmonary arteries are the vessels most severely damaged and that lesions never occur in the cerebral vessels and are rare in the peripheral and renal arteries and in the other branches of the abdominal aorta; (2) the lesions in rabbits resemble the early stages of arteriosclerosis in humans but the more advanced types of lesions do not develop; (3) cholesterol feeding does not result in significant hypercholesterolemia and arterial lesions in omniverous animals such as the dog, cat, rat or monkey. It has therefore been argued that the lesions produced in the rabbit are simply the response of an herbiverous animal to a substance which is not normally present in its diet and for which it has no effective metabolic pathway.

In contrast to the rabbit, chickens and many other birds do have spontaneous arteriosclerosis. Intimal lesions are almost always found in the arteries of aged chickens. In distribution and morphology these lesions closely parallel those seen in man. The underlying cause of these spontaneous lesions in the chicken is as much of a mystery as is the cause of human arteriosclerosis. However, it has been shown that raising the serum cholesterol level in young cockerels either by feeding them cholesterol or by administering stilbestrol results in the premature development of arteriosclerosis.

The occurrence of spontaneous intimal lesions in dogs is rare but not unknown. It was as high as 5 per cent in some series of old dogs. Many attempts in the past to produce arteriosclerosis in dogs by feeding them large amounts of cholesterol failed and in no case could a sustained hypercholesterolemia be maintained. However, in a recent report from this laboratory[8] it was demonstrated that if the function of the thyroid gland of dogs was modified by thiouracil administration, the feeding of cholesterol resulted in greatly elevated serum cholesterol levels. Maintenance of this hypercholesterolemia for a period of twelve to sixteen months resulted in lesions similar in distribution and morphologic characteristics to those seen in human

[8] STEINER, A. and KENDALL, F. E. Atherosclerosis and arteriosclerosis in dogs following ingestion of cholesterol and thiouracil. *Arch. Path.*, 42: 433, 1946.

arteriosclerosis. I would like to present this work in some detail.

Our first study involved four mongrel dogs. All of these animals were given thiouracil in doses starting at 0.5 Gm. and increasing to 1.2 Gm. per day. It was observed that from a control serum cholesterol level of 150 to 160 mg. per cent, the levels rose to 210 mg. per cent during the two months on thiouracil. At this point cholesterol was added to the diet of three of the dogs in the form of 10 Gm. of cholesterol in 40 cc. cottonseed oil daily. The serum cholesterol levels of these animals then rose progressively over the course of the next fourteen months to peaks of 932, 1,134 and 2,176 mg. per cent. During this time one dog had remained on thiouracil alone and showed a serum cholesterol level which averaged 284 mg. per cent. When the dogs were sacrificed after twelve to fourteen months of this hypercholesterolemia, the three cholesterol-fed animals showed arteriosclerotic lesions which were similar to human lesions in distribution and morphology. The dog which had received thiouracil without cholesterol showed no arterial lesions.

We have been able to repeat these results in young dogs of known age and antecedents. A group of four littermate mongrel dogs born in our laboratory was started on cholesterol feeding at the age of four months. This time the daily 10 Gm. of cholesterol was dissolved in ether, then applied to the dry diet of Spratt's meat fibrine dog cakes and the ether allowed to evaporate. This left the cholesterol well distributed throughout the food in finely divided form and obviated the high fat intake occasioned by the cottonseed oil used in our first series of dogs. Analysis of the feces indicated that from 60 to 80 per cent of this cholesterol was absorbed. During this cholesterol feeding period the serum cholesterol rose to 400 to 500 mg. per cent. After four weeks on cholesterol alone two of the dogs were in addition given thiouracil, starting with 0.8 Gm. per day and increasing finally to 1.2 Gm. per day. The other two dogs were kept on cholesterol but were given no thiouracil. The serum cholesterol level of the "cholesterol" dogs averaged 400 mg. per cent. The average levels of the

FIG. 5. Dog arteriosclerosis; abdominal aorta showing multiple intimal plaques which coalesce about the exit of the branches. The circular muscle bundles of the iliac arteries are accentuated by the plaques.

6 7

FIG. 6. Dog arteriosclerosis; an early lesion in the thoracic aorta. Two distinct layers of atheromatous deposits are apparent. The internal elastica is intact but lipid has infiltrated to the media beneath the plaque giving the upper portion a loose vacuolated appearance; elastic tissue stain, × 163.

FIG. 7. Dog arteriosclerosis; iliac artery; a typical plaque with foam cells and fibrosis. Vacuolated spaces representing lipid appear in the media. The internal elastica is visible at the left but disappears beneath the fibrotic area of the plaque; hematoxylin and eosin stain, × 163.

"cholesterol-thiouracil" dogs for the sixty weeks were 1,089 and 1,206 mg. per cent.

When the cholesterol-fed controls were sacrificed after seventy-two weeks, one showed no arterial lesions. The other dog, which had almost identical serum cholesterol levels, showed several fine, raised yellow streaks in its abdominal aorta. On microscopic section these were seen to consist of lipid depositions beneath the aortic intima, forming an early arteriosclerotic plaque.

Autopsy of the two "cholesterol-thiouracil" dogs after sixty weeks revealed extensive generalized arteriosclerosis in both animals. The lesions varied from small, pin-point, yellowish elevations of the intima to large, coalescing plaques. Lesions were most marked in the abdominal aorta and its branches. Figure 5 shows the gross appearance of one of these aortas, with the most advanced lesions in the abdominal aorta and its branches. Lesions were also present in the thoracic aorta, iliac, femoral, coronary, innominate, thyroid, subclavian, mesenteric and renal arteries and in the sinus of Valsalva. For the first time cerebral lesions were found about the circle of Willis in both of these dogs. Microscopically, the lesions showed almost all of the features of human arteriosclerosis. Figure 6 shows an elastic tissue stain of an aortic lesion. This is an early lesion. The intima is raised with fat-laden foam cells. Some fat-laden cells are apparent in the media beneath the as yet intact internal elastica. A section of a typical iliac artery plaque (Fig. 7) shows the marked thickening of the intima with fibrosis and fat-laden cells penetrating into the media. The coronary arteries (Fig. 8) show arteriosclerotic lesions which replace much of the media, thicken the intima and narrow the lumen. In the larger artery you can see most of the morphologic

FIG. 8. Dog arteriosclerosis; coronary artery; showing many of the sequelae of human arteriosclerosis. The lumen is narrowed by diffuse atheromatous deposits. Within the plaques are hemorrhage, hyalinization and calcium. The media has been partially replaced by lipid deposits; hematoxylin and eosin stain, × 86.

features of an advanced human lesion including hemorrhage within the plaque, hyalinization, and about the outer margin of the lesion a thin, bluish line of calcification. In the middle cerebral artery (Fig. 9) the lesion is apparently limited to the intima with considerable narrowing of the lumen. Such cerebral lesions were present in both of our last "cholesterol-thiouracil" dogs.

It is clear, then, that arteriosclerosis can be produced in an omnivorous mammal, the dog, by feeding cholesterol and thiouracil. The resultant lesions have the same anatomic distribution and sites of predilection as those in man, including involvement of coronary, renal and cerebral arteries. The dog lesions have most of the morphologic features of human arteriosclerosis, including hyalinization, hemorrhage and calcification. In no case thus far, however, has ulceration into the lumen of the artery been observed.

Thiouracil in the doses used does not itself lead to arterial lesions. In one instance early arteriosclerotic lesions developed following the feeding of 10 Gm. cholesterol

FIG. 9. Dog arteriosclerosis: middle cerebral artery. Intimal atheromatous deposits narrow the lumen. Fibrous tissue beneath the endothelium and at the edges of the larger plaque is encroaching upon the foam cells; hematoxylin and eosin stain, × 144.

per day in a diet otherwise containing less than 5 per cent fat and without thiouracil.

Although our series of arteriosclerotic dogs is still too small to permit any positive correlation of the degree of hypercholesterolemia with the extent of the lesions, it is interesting to note that no lesions have been found in dogs in which the serum cholesterol level was less than 400 mg. per cent for twelve months. Above this level, without exception, the higher the serum level (over the 12- to 14-month period) the more extensive was the arteriosclerosis found at autopsy. Experiments are in progress to quantitate further the degree and duration of the hypercholesterolemia necessary for the production of arterial lesions.

STUDENT: I would like to ask how far it was necessary to depress the basal metabolic rate in the dogs that developed arteriosclerotic lesions on the combined cholesterol-thiouracil regimen.

DR. SEEGAL: Dr. Davidson has determined the basal metabolic rate in some of these dogs and can give us that information. I hope he will tell us about the methods he employed because determining the basal metabolic rate in dogs proved to be a more difficult feat than was anticipated.

DR. JACK D. DAVIDSON: The basal metabolic rate was not determined in the dog

experiments described by Dr. Kendall but they are currently being determined in a similar group of dogs receiving 1.2 Gm. thiouracil per day. The basal metabolism is estimated by the use of a standard clinical type of Sanborn machine adapted to the dog by the use of a pneumatic cushioned muzzle mask which gives an air-tight seal when applied to the shaven and lubricated muzzles. Light sodium pentobarbital hypnosis is used to obviate the long period of training otherwise required. This light hypnosis has been shown by Cavett and by Galvão to have no perceptible effect upon the basal metabolic rate of the dog. In our animals 13 mg. of sodium pentobarbital per Kg. body weight given intravenously causes hypnosis which is light enough to be interrupted by any painful stimuli and which terminates with the dog spontaneously lifting his head after twenty to forty minutes. Since there is considerable disagreement as to standard basal metabolic rates for dogs, due to poor correlation of caloric production with physical measurements and the confusion caused by species differences and different types of hair, we have used the results of control Sanborn measurements on each dog prior to thiouracil feeding as the normal standard or "0" per cent for that animal. Subsequent variation has then been expressed as a percentage of this normal value for the given dog. On this basis the animals on this experiment have shown basal metabolic rates which are −15 to −20 per cent. The animals do not look or act myxedematous and show normal growth; but their tolerance to sodium pentobarbital has definitely diminished as their basal metabolic rates declined, and their tolerance to cold is below normal as shown by shivering under conditions that do not cause normal dogs to shiver.

STUDENT: Have you tried to produce arteriosclerosis in rats or mice?

DR. KENDALL: We have tried to produce lesions in rats by combined cholesterol-thiouracil feeding but failed to produce sustained hypercholesterolemia of significant degree and no atheromas were apparent either grossly or microscopically.

STUDENT: Have you any explanation for these species differences?

DR. KENDALL: No.

DR. KENNETH B. TURNER: There are interesting differences in the response to cholesterol feeding not only between animals of different species but also between different animals of the same species. For example, in experiments carried out some years ago we found marked individual differences among our rabbits with respect to the maximal level of cholesterol in the blood after feeding the same amount of cholesterol. In one animal it might never rise above 300 mg. per cent while in another receiving the same amount of cholesterol over the same period the level might rise to 1,200 or 1,300 mg. per cent. Eventually, however, the level of cholesterol in the blood of each animal reaches an irregular plateau. This would seem to indicate that the animals somehow acquire the ability to metabolize or excrete the large amounts of cholesterol administered and thus achieve a state of equilibrium. An occasional rabbit displays from the start surprising capacity to handle exogenous cholesterol so that after several months of feeding only a slight elevation of the blood cholesterol has occurred. This so-called "resistance" is abolished by thyroidectomy. In the otherwise normal rabbit thyroidectomy results in only a slight rise in serum cholesterol; but when performed in a cholesterol-fed but "resistant" rabbit, there is prompt disappearance of the "resistance," with development of marked hypercholesterolemia.

The experience with rabbits in the production of atherosclerosis by cholesterol feeding coincides with that indicated by Dr. Kendall in dogs. Atherosclerosis does not occur in the rabbit without antecedent elevation of the blood cholesterol; to this there are no exceptions provided one excludes medial sclerosis, a quite distinct lesion which may occur "spontaneously." Hypercholesterolemia without atherosclero-

sis, on the other hand, is observed in cholesterol-fed rabbits although infrequently.

When a rabbit fed cholesterol for a sufficient period of time is autopsied, certain lesions in addition to the atheromatous changes in the aorta are obvious upon gross

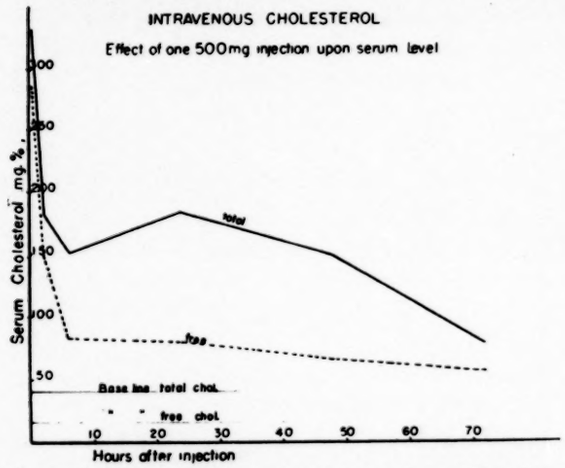


FIG. 10. Serum cholesterol levels in the rabbit after intravenous injection of cholesterol suspension. Note the rise in total cholesterol at the twenty-four-hour interval while the free cholesterol is unchanged. The rise is due entirely to an increase in cholesterol esters.

examination. There is a fatty liver, the adrenals are large and there are fatty deposits in the spleen and kidneys. This simultaneous development of lipoidosis has been cited as a point of dissimilarity between the atherosclerosis of rabbit and man. However, if cholesterol feeding is discontinued after a sufficient period of hypercholesterolemia, the blood cholesterol gradually drops to normal levels; and if the animals are sacrificed at this time, the gross findings at autopsy may be quite different. The atheromas persist but the visceral lesions are slight or absent. It should be emphasized that in this situation one finds atherosclerosis associated with normal levels of cholesterol in the blood at the time the animal is sacrificed.

DR. BEVANS: It might be worth pointing out that in such rabbits, although lipoid is continually absorbed from the aortic lesions, plaques may be discernible for as long as three years after cholesterol feeding has ceased and the serum cholesterol has returned to base line levels.

DR. SEEGAL: Because of uncertainties in the absorption of the cholesterol fed these experimental animals by mouth, investigators have long been interested in producing atherosclerosis by intravenous injection of cholesterol suspensions. These attempts were unsuccessful until about two years ago when Dr. Kendall prepared an emulsion of 2.5 per cent cholesterol stabilized in 0.5 per cent sodium stearate and found that this suspension could be injected into the ear veins of rabbits without difficulty. It has been possible in this way to produce lesions indistinguishable in appearance and distribution from those of animals fed similar amounts of cholesterol over the same period of time. The results have been especially illuminating in clarifying the morphologic sequence of events in the genesis of arteriosclerotic plaques and I have asked Dr. Bevans to tell us about these experiments.

DR. BEVANS: We have followed the blood levels and the development of these lesions and I will describe some of our results. After a single injection of 0.5 Gm. of colloidal cholesterol, blood levels were determined at intervals of ten minutes, six hours, twenty-four hours and forty-eight hours. A sample curve is shown in Figure 10. It is apparent that the secondary rise in total cholesterol which consistently occurs at the end of twenty-four hours is due to a rise in the ester fraction and not in the free cholesterol. This suggests that the injected cholesterol is cleared from the blood and then slowly returned after esterification. A close relationship between the chemical and histologic findings exists since the amount of lipoid in the parenchymal cells of the liver reaches its peak at twenty-four hours and decreases from that time on. At the end of six days the serum cholesterol returns to base line values. It is possible to repeat the curve in the same animal many times.

When five injections a week of 0.5 Gm. of cholesterol each were given, the serum cholesterol levels attained were of the same order as those observed in rabbits fed the

same amount of cholesterol in their diet. (Fig. 11.) It will be noted also that the rate of disappearance is approximately the same in each group. As early as three hours after the first injection of 0.5 Gm. of cholesterol, lipoid is visible within the intima of the aorta. It first appears within the endothelial cells which are swollen and prominent. At the end of twenty-four hours more lipoid is visible in the endothelial cells and has spread to the intercellular substance. No intimal proliferation has occurred. At seventy-two hours less lipoid is present in the intima but cellular proliferation is evident. By this time lipoid has penetrated the internal elastica and the upper layers of the media. The endothelial cells are foamy. During these early phases the vasa vasorum of the outer media and adventitia are diffusely stained with lipoid. This is no longer apparent after the seventy-two-hour period except for a few sudanophilic droplets in an occasional intimal endothelial cell of the small vessels. That the lipoid material observed in the intima does not enter via the vasa vasorum can readily be seen in those areas where the intimal accumulation is far removed from these vessels.

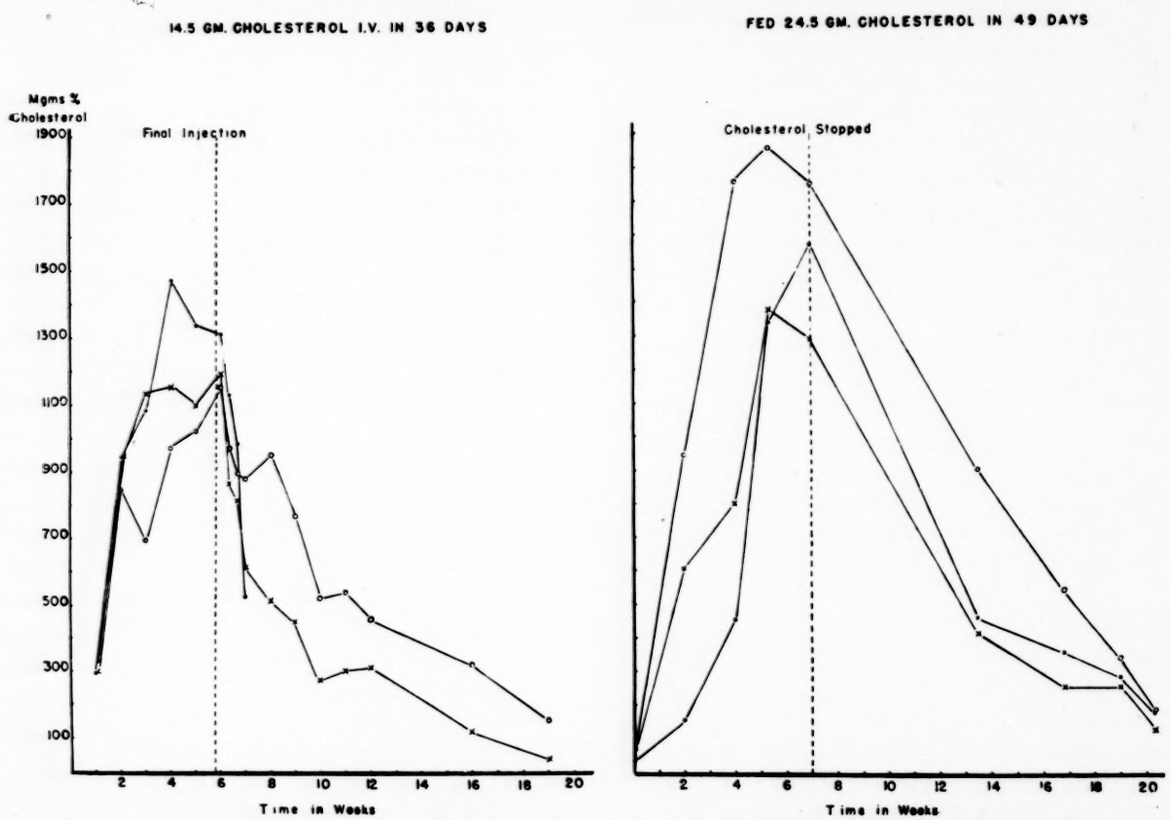


FIG. 11. Comparison of serum cholesterol levels after injection or feeding of cholesterol in rabbits. Note that the animals were fed for forty-nine days while the other group was injected for thirty-six days. At the thirty-six-day interval the serum cholesterol levels are similar.

As the interval after the single injection lengthens, less and less lipoid is present within the intima but the proliferation of intimal cells continues to be present for at least two months. At the end of six months all lipoid has disappeared and no intimal proliferation can be found.

When rabbits are given twelve daily injections of 0.5 Gm. of the cholesterol suspension, the first gross lesions can be identified in the ascending aorta. Microscopically, these lesions are well developed atheromatous plaques with abundant lipoid. Sudanophilic material can be followed through the media into the peri-aortic tissues. (Fig. 12.) When rabbits are given

FIG. 12. Plaque in intima of ascending aorta noted grossly after twelve daily injections totaling 6 Gm. of colloidal cholesterol. The rabbit was sacrificed one month after the last injection. Lipid can be traced through the media and has collected in the adventitial and peri-aortic connective tissue; Sudan IV stain, × 125.

thirty-six injections over a six-week period, the lesions are much larger and more numerous. As has been stated before they are indistinguishable in number, appearance and distribution from those seen in animals fed the same amount of cholesterol (18 Gm.) over the same period of time. Whether these animals are sacrificed immediately or six months later makes little difference in the appearance of the lesions.

Lipoid found elsewhere in the organs is in proportion to the amount injected. Within three hours after a single injection, small amounts are found in the Kupffer cells of the liver but very little in the parenchymal cells. The sudanophilic droplets are more numerous after twenty-four hours when they are present also in the endothelial cells of the portal veins and stain the entire wall of the vein diffusely. Some of the lipoid has migrated to the perivascular tissue and appears in the connective tissue cells. At three hours there is little lipoid in the parenchymal cells but this increases up to twenty-four hours. Following this there is a decline until at the end of a month only small droplets remain in the Kupffer cells. About the same amount is present at the end of six months. In the kidney, at the end of twenty-four hours following a single injection, the blood vessel walls and glomerular capillaries are flooded with sudanophilic material. Numerous droplets are present in the tubular epithelium. At the end of a week glomeruli no longer contain lipoid and only small amounts remain in the tubular epithelium. In the lungs and spleen a similar flooding of endothelial cells of the large vesse'.s and walls of the capillaries is observed. Despite the large quantities of emulsion injected we have never observed large pulmonary emboli.

As larger amounts of cholesterol are injected, more and more lipoid accumulates and remains for longer periods. It is evident that cholesterol is taken up through the body of the rabbit by the reticuloendothelial system but it is also evident that it remains in the intima of the aorta long after it is cleared elsewhere.

Since lipoid can be detected in the intima of the aorta within three hours following injection of cholesterol suspension, these experiments suggest direct penetration of the intact endothelium by lipid in the development of atheromatous plaques. It would be difficult to reconcile these observations with Leary's hypothesis that fat-laden Kupffer cells of the liver migrate to the wall of the aorta to form the nidus of an atheroma.

DR. SEEGAL: It is clear that the experimental production of arteriosclerosis in animals has already thrown much light upon the problem of arteriosclerosis in man. This would be even more evident if we were able to present the work of other investigators in this field but time does not permit. We must go on to consider the clinical aspects of the problem. Dr. Steiner has for some years been working on the relationship of human arteriosclerosis to cholesterol metabolism and I have asked him to summarize his experience.

DR. ALFRED STEINER: The range of serum cholesterol values in normal human subjects is wide. The two technics most widely used are those of Bloor, in which the range of normal cholesterol varies from 175 to 300 mg. per 100 cc., and the method of Schoenheimer and Sperry, in which the range

varies from 150 to 275 mg. per 100 cc. The method of Schoenheimer and Sperry is considered to be more accurate although it is technically difficult and requires considerable facility before reproducible results are obtained. The ratio of ester to free cholesterol is constant, approximately 3 to 1.

In a study with Dr. K. B. Turner it was demonstrated that in a group of relatively normal persons the individual serum cholesterol levels remain quite constant from hour to hour, day to day and month to month during the period of a year. The deviation from the mean cholesterol level for each patient was less than 10 per cent.

In well documented coronary arteriosclerosis the results of serum cholesterol determinations have given inconclusive results. Several reports record an elevation of serum cholesterol while others do not. In our own studies frequent consecutive determinations of serum cholesterol for periods up to two years were made in fifteen patients with coronary arteriosclerosis. Thirteen of these patients had had a typical coronary thrombosis; the remaining two individuals had angina pectoris with a positive anoxemia test for coronary insufficiency. The patients were not included in this study until at least six weeks had elapsed since the onset of the myocardial infarction. A total of 914 serum cholesterol determinations were made, 572 on the patients with coronary arteriosclerosis and 342 in the normal individuals. The average serum cholesterol of the patients with coronary arteriosclerosis was found to vary from 308 to 499 mg. %, with a mean for the group of 355 mg. %; the standard deviation for the patients was 24.8. In contrast the average serum cholesterol values for each of fifteen relatively normal individuals varied from 214 to 334 mg. %, with a mean average of 254 mg. % for the group. The fluctuations of the serum cholesterol, as measured by the standard deviation, for the normal subjects averaged 8.7, about one-third of that of the patients with coronary arteriosclerosis.

Although statistically these results are significant, it was believed desirable to have serum cholesterol determinations on a larger group of patients. For this reason a single serum cholesterol determination was made in fifty additional patients with coronary arteriosclerosis and in fifty additional normal persons of the same age group. The average serum cholesterol value for the second group of patients with coronary arteriosclerosis was 336 mg. % in contrast to 236 mg. % for the control subjects. These results confirmed the previous observations.

Since these studies were reported, Lerman and White found that twenty-two of twenty-eight patients with coronary arteriosclerosis under the age of forty had an elevation of serum cholesterol. Boas also has reported that an elevated serum cholesterol is a frequent finding in patients with coronary arteriosclerosis and furthermore in members of the families of these individuals.

In summary, the serum cholesterol level of patients with overt coronary arteriosclerosis is significantly higher than that of normal subjects of the same age group. Moreover, the serum cholesterol level of patients with coronary sclerosis fluctuates much more widely than in the normal subject.

A number of possible factors that might influence the serum cholesterol levels in human subjects have been studied. The administration of potassium iodide, a favorite of the older clinicians in the treatment of arteriosclerosis, has been shown to have no effect on the serum cholesterol level. Four and one-half grains of thyroid extract daily, however, resulted in a lowering of the serum cholesterol level approximately 90 mg. per cent in four to five weeks, associated with an increase in the basal metabolic rate of approximately 21 per cent. The post-thyroid period was of interest in that the serum cholesterol level overshot the normal level and remained elevated for two to four weeks. The feeding of soya lecithin results in a temporary lowering of serum cholesterol in normal individuals as well as in those with hypercholesterolemia associated with xanthomatosis.

The effect of an infection, pneumonia, on the serum cholesterol level was studied. Serum cholesterol estimations were made at frequent intervals during and subsequent to pneumonia in nineteen patients. The presence of *hypo*cholesterolemia during the acute phase of the pneumonia was confirmed. It was further noted, however, that a subsequent *hyper*cholesterolemia associated with wide fluctuations occurred during convalescence before the characteristic stable individual serum cholesterol level was reestablished. In the patients studied the increase in serum cholesterol over the normal level varied from 20 to 250 mg. per cent, averaging 82 mg. per cent. The duration of the elevated and inconstant serum cholesterol values averaged fifty-two days. It is conceivable that such a period of transient hypercholesterolemia might lead to deposits of cholesterol in the arteries.

The effect of diet on serum cholesterol would appear to have considerable significance in view of some of the experiments described today. Leary, and more recently Dock, have advocated the restriction of dietary cholesterol so as to prevent or retard the development of arteriosclerosis. The rationale for this suggestion was based chiefly on the experimental arteriosclerosis produced by excess feeding of cholesterol. However, there are other data which tend to suggest that diet has an important bearing on the development of arteriosclerosis. In China, Okinawa and Costa Rica, where poor nutrition is prevalent, a low incidence of arteriosclerosis has been reported. The diet in these countries is characteristically low in cholesterol, protein and calories and is made up chiefly of carbohydrates of vegetable origin.

The tendency for individuals who are obese to succumb more commonly to sequelae of arteriosclerosis and coronary or cerebral occlusion has been noted by analysis of statistics by life insurance companies. French and Dock stated that seventy-three of eighty young soldiers dying of coronary arteriosclerosis had some degree of obesity.

It was therefore considered of interest to determine the effect of diets rich or poor in dietary cholesterol on the serum cholesterol level. In the first phase of this study the response of the serum cholesterol of thirty-five patients, with various diseases, to a single meal rich in fat and cholesterol was determined. The method of study was as follows: blood for analysis was taken at 8 A.M. with the patient in the fasting state. Breakfast consisted of fruits, two eggs, buttered toast, coffee and 200 cc. of milk to which 20 Gm. of cholesterol had been added. Dinner and supper were served at the usual hours. Additional blood samples were taken at 10 A.M., noon, 4 P.M. and 8 A.M. the following day. The results showed clearly that little or no change in the serum cholesterol occurred during the course of twenty-four hours, regardless of the feeding of a large amount of cholesterol.

In the second phase of this study nine individuals were placed on diets high or low in fat and cholesterol. They were first given a diet containing 300 Gm. of fat for six weeks and then without interruption placed on a diet containing less than 50 Gm. of fat. In five of the nine patients there was no increase in total serum cholesterol during the period of high fat feeding. In four cases a slight rise seemed to occur. Three of the patients subsequently were placed on the high fat diet for a second period but this time 10 Gm. of cholesterol in 200 cc. of milk was added to the regimen. No significant change resulted in the serum cholesterol levels.

The serum cholesterol levels of the patients on a low fat diet were no different from those observed during the control period.

This study has recently been repeated in four patients with coronary arteriosclerosis. After an initial control period the patients were given 100 Gm. of egg-yolk powder (roughly the equivalent of twelve egg yolks) containing 3 per cent cholesterol daily for six weeks. At the end of this time the diet was changed to one low in cholesterol (butter, cream, egg yolk and fatty meats

were excluded) for six additional weeks. Only slight increases in the serum cholesterol levels were found during the egg-yolk feeding period. It was possible in this experiment to estimate the quantity of cholesterol actually absorbed and metabolized by determining the amount of sterol excreted in the stool. No significant differences in the sterol excretion occurred during initial control and high or low fat and cholesterol diet periods. It can therefore be assumed that the dietary cholesterol was absorbed and either metabolized or laid down in the tissues. With the serum cholesterol and fecal sterol content essentially unchanged, one might infer that the mechanism of cholesterol turnover in the body is very active and able to handle large amounts of exogenous cholesterol. If this were not so, a marked elevation of serum cholesterol would be expected on a high cholesterol diet and, conversely, a fall in the serum cholesterol on a low cholesterol diet. Further studies of this problem by the isotope technic are indicated.

In the third phase of the effect of diet on serum cholesterol, ten patients with well documented episodes of coronary thrombosis were placed on a low cholesterol diet for periods from four to fourteen months. Butter, egg-yolk, cream and fatty meats were excluded from the diet during the low cholesterol regimen. Oleomargarine, a vegetable fat, was allowed. The patients were followed in the out-patient department so strict adherence to the diet may not have been observed; however, all the patients were most cooperative. Serum cholesterol determinations were made at intervals of two weeks or at monthly intervals. Preliminary results of this study indicate that the serum cholesterol levels of five of the ten patients were lower than those observed in the initial regular diet period. Considerable fluctuations of the serum cholesterol level occurred during the period of regular diet but seemed to be less variable during the low cholesterol diet period. It was not possible to judge adequately whether this low cholesterol ingestion resulted in any change in the clinical status of the patients.

The recent demonstration by Rittenberg and his co-workers that cholesterol can be synthesized in the body from acetate—a substance formed in the metabolism of fat and possibly from glucose and protein—is pertinent to the problem of reduced cholesterol intake. If the body synthesizes excessive amounts of cholesterol, the restriction of dietary cholesterol intake would be of little avail. However, the overburdening of an already disturbed cholesterol metabolism by excessive cholesterol ingestion might be harmful. Further studies are necessary before a final evaluation of this problem can be made.

DOCTOR: Arteriosclerosis is frequently found in subjects who have serum cholesterol levels within the normal range and who have no history of recognized hypercholesterolemia in the past or any disease associated with hypercholesterolemia. They also have normal basal metabolic rates. Production of arteriosclerosis in animals in the experiments described by Dr. Kendall, however, required the sustained maintenance of marked hypercholesterolemia over long periods by instituting experimental conditions which so far as we know do not obtain in most clinical cases of arteriosclerosis. This raises the question in my mind as to how relevant the animal work is to the clinical problem of arteriosclerosis.

DR. KENDALL: The great resemblance between the lesions seen in clinical arteriosclerosis and those produced experimentally, particularly in the dog, leads us to believe that they are fundamentally alike. The failure to find a history of hypercholesterolemia in much of the clinical material suggests that it would be well to look beyond the high serum cholesterol levels in the experimental animals for the real cause of arteriosclerosis. It is possible that initiation of the lesion in both experimental animals and in human beings is not due to high cholesterol levels *per se* but to the presence of some abnormal

substance related to cholesterol. Although various oxidation products of cholesterol which may be intermediate compounds in its metabolism have been isolated from lesions of human aortas, very little is known about the role they may play in arteriosclerosis. Our laboratory has started an investigation of the physiologic significance of some of these compounds but all such work is seriously hampered by the inadequacy of available information concerning the intermediary metabolism of cholesterol, the way it is built up and broken down in the body. Further extension of isotope technics to obtain this fundamental information is urgently needed.

Another point which may be relevant to this discussion is the fact that the cholesterol of the serum is for the most part not in true solution but in colloidal suspension stabilized by the other lipids and the proteins of the serum. Normally only a small portion of this cholesterol can be extracted from the serum with organic solvents. In hypercholesterolemia occurring both in human beings and in experimental animals a large part of the cholesterol can be extracted. There has been a change in the physical state as well as in the amount of cholesterol present. It may develop that this change in physical state is one of the factors responsible for the development of atherosclerosis.

DR. STEINER: I do not think that the finding of arteriosclerosis in individuals who have had one or two casual serum cholesterol determinations within the normal range, a normal B.M.R. on one or more occasion, and who have not had one of the usual diseases associated with hypercholesterolemia (poorly controlled diabetes, myxedema, chronic nephritis or xanthomatosis), invalidates the significance of cholesterol in arteriosclerosis. That the serum cholesterol in relatively normal persons ordinarily remains quite constant so far as we know (the longest available study of serum cholesterol levels in normal subjects did not extend beyond a two-year period) does not rule out the possibility that periods of hypercholesterolemia as well as of instability of the serum lipids may occur in the lifetime of some individuals. Certainly the demonstration that following an acute infection such as pneumonia the serum cholesterol level, after a period of hypocholesterolemia during the febrile phase, becomes elevated and extremely labile for periods up to three to six months, is a specific example of one of the factors influencing the serum cholesterol pattern during the lifetime of an individual. The serum cholesterol pattern may also be altered by other conditions, such as endocrine and dietary factors. It is quite possible that deposition of cholesterol in the walls of arteries may occur during such transitory periods of hypercholesterolemia. It would certainly seem significant that in all of the usual diseases that are associated with widespread and premature arteriosclerosis an elevation of serum cholesterol has been found, providing the study is adequate and carried on over a sufficiently long period. The fact that arteriosclerosis occurs in patients who have not been found to have elevated serum cholesterol levels may indicate only that our data are incomplete.

Another factor to be considered is the wide range of the normal serum cholesterol. If one individual's serum cholesterol ordinarily is 160 mg./100 cc. and is then increased to 250 mg., still a normal figure, I think we would have to say that this alteration was a significant one, and might be associated with infiltration of cholesterol into the tissues.

DOCTOR: Have you gotten any leads from the animal work that could be applied to the clinical problem of preventing or minimizing arteriosclerotic lesions in man?

DR. STEINER: Of course the ultimate aim of the animal work is just that. At present we are building up a large dog colony for the purpose of standardizing the conditions necessary to induce arteriosclerosis in dogs so that we can systematically test out the various possibilities in prevention of the lesions under adequately controlled conditions. Experiments with lipotropic agents

such as choline, which appears to have a preventative effect in rabbit arteriosclerosis,[9] have already been extended to dogs but we are not yet able to give you any results. In the meantime we are continuing our clinical observations, our attempts to lower serum cholesterol levels particularly in subjects with coronary sclerosis by dietary measures. As we learn more about the dietary precursors of cholesterol in man and about the intermediary metabolism of cholesterol, we can direct these efforts more intelligently.

In any event, with the realization that arteriosclerosis is not an inevitable concomitant of aging but may be due to factors that can be controlled, investigation in this field has become more aggressive. We believe that sufficient progress has been made to justify further intensive efforts to prevent or minimize arteriosclerosis in man.

SUMMARY

DR. ALEXANDER B. GUTMAN: In view of the fact that arteriosclerosis in one or another of its complications and sequelae is responsible for more disability and death than any other disorder, it is surprising how little has been discovered concerning its causes, natural history, prevention and treatment. This has been due in large part to the general attitude of apathetic acceptance of arteriosclerosis as an inevitable consequence of aging. Moreover, such efforts as have been made to attack the clinical problem have been largely frustrated by inadequate methods of diagnosis except upon presumptive evidence or by the indications of late complications; the impossibility of quantitation of arteriosclerotic lesions during life; and the difficulty in distinguishing clinically between intimal and medial sclerosis, two distinct abnormalties.

In recent years a more aggressive attitude toward the problem of arteriosclerosis has evolved. This has, in large part, grown out of the successful production of atherosclerosis in experimental animals, first in rabbits by Anitschkow, more recently in guinea pigs, chickens and dogs; in the dog (like man, an omnivorous mammal) the lesions produced are reasonable facsimiles of human arteriosclerosis as regards morphology, distribution and sites of predilection. The experimental reproduction of these lesions in young animals has encouraged the view that human arteriosclerosis may be due to factors that can be controlled.

Experimental atherosclerosis is produced by the administration of large amounts of cholesterol with consequent marked hypercholesterolemia (in the case of the dog it has been necessary also to depress thyroid function with thiouracil). This has focused attention upon the possible role of cholesterol in the pathogenesis of human arteriosclerosis. There are other reasons for this special interest in cholesterol: (1) In human arteriosclerosis the earliest detectable lesions are deposits of lipids in the intima. Chemical examination of the lipids obtained from arteriosclerotic human aortas has disclosed that cholesterol constitutes 40 to 65 per cent of the phospholipid-free fat content; in addition there are small amounts of at least four oxidation products of cholesterol and one reduction product. (2) Arteriosclerosis not infrequently develops prematurely and with great severity in such diverse diseases as poorly controlled diabetes mellitus, xanthomatosis, nephrosis and myxedema which have in common a marked increase in the blood lipids, particularly cholesterol. It has therefore seemed justifiable to limit this clinic largely to a consideration of cholesterol and its derivatives, referring to the reviews of Cowdry,[1] Duff,[2] Winternitz,[3] Hueper[4] and a recent Biological Symposium[5] for a more comprehensive discussion of arteriosclerosis. Another excellent general review of arteriosclerosis, by Gubner, will be found in the review section of this issue of the American Journal of Medicine.

Cholesterol is a sterol, quantitatively by far the most important animal sterol and almost universally distributed in animal

[9] STEINER, A. Effect of choline in the prevention of experimental aortic atherosclerosis. *Arch. Path.*, 45: 327, 1948.

tissues. Its function, however, is not known except insofar as it serves as a precursor of related physiologically active sterols. Part of the cholesterol in the body is absorbed from the preformed cholesterol of the diet but cholesterol is not an essential dietary constituent since, as is now clear, it can readily be synthesized by the body. Isotope technics have recently disclosed that acetate is an important precursor of cholesterol and that acetone is probably a source of the methyl groups. Neither acetate nor acetone as such are common constituents of the diet but large amounts are formed in the metabolism of fatty acids and ketogenic amino acids. Moreover, since carbohydrates are readily converted into fats in the body, it would appear that any dietary constituent may act as a precursor of cholesterol. This recent realization has important implications in attempts to control human arteriosclerosis by dietary measures.

Much of the remainder of this Clinic was devoted to a detailed presentation of the experimental production of atherosclerosis in dogs and rabbits by a group at the Columbia Research Service at Goldwater Memorial Hospital. Lesions were produced in young dogs by feeding 10 Gm. cholesterol daily in a standard diet otherwise containing less than 5 per cent fat, and simultaneously giving sufficient thiouracil to reduce the basal metabolic rate to about −15 to −20 per cent as compared with the control level. This regimen was maintained for about a year during which time marked hypercholesterolemia (average levels in excess of 1,000 mg. per cent) persisted. At necropsy extensive and advanced arteriosclerosis was found in these young dogs, including involvement of the aorta, coronary, renal and cerebral arteries. The fidelity with which arteriosclerosis in man was reproduced is evident from the photomicrographs which illustrate extension into the media, hyalinization, hemorrhage and calcification although no ulceration into the lumen of the artery has yet been observed.

The rabbit experiments described are of interest because they represent the first successful attempt to produce atheromatosis by intravenous injection of stable cholesterol emulsions, specifically of 2.5 per cent cholesterol stabilized in 0.5 per cent sodium stearate. The results of this technic have shed much light upon the morphologic sequence of events in the genesis of arteriosclerotic plaques. Upon injection the cholesterol is rapidly taken up by the cells of the reticuloendothelial system throughout the body. Particularly large amounts of lipid appear in the liver, first in the Kupffer cells, then in the parenchymal cells from which it gradually disappears, probably after esterification and other metabolic changes have been effected. In the intima of the aorta, lipid can be detected within three hours of injection, suggesting direct penetration of the intact endothelium by the lipid. But whereas the lipid eventually disappears from most tissues without leaving a recognizable trace or scar, its appearance in the intima initiates a characteristic sequence of tissue reactions resulting in what we designate an atheromatous plaque, which persists for a long time. These facts have implications of interest in human arteriosclerosis.

Impressive though these experimental results are, it must be recognized that they are produced under conditions which have no counterpart in human arteriosclerosis. The amounts of cholesterol fed or injected are enormous relative to human dietary consumption of cholesterol; and in the dogs the basal metabolic rate must be reduced well below that of most clinical cases of arteriosclerosis. Marked and sustained hypercholesterolemia was a *sine qua non* in the experiments described whereas arteriosclerosis occurs frequently in human subjects with serum cholesterol levels within the normal range and with no history of recognized hypercholesterolemia in the past or any disease associated with hypercholesterolemia. It may therefore be hazardous to draw too literal an analogy between the mechanisms of experimental and clinical arteriosclerosis.

The differences, however, may well be quantitative rather than qualitative. It is evident that there are important species differences with regard to effective metabolic pathways for cholesterol. Man is predisposed to arteriosclerosis, to judge by the frequency of human arteriosclerosis as compared with the uncommon "spontaneous" occurrence of intimal atheromatosis in old rabbits and dogs. It may well be that the factors operating in experimental cholesterol atheromatosis in the rabbit and dog (and these are deliberately intensified to accelerate the production of maximal lesions) are needed in much lesser degree to provoke arteriosclerosis in man; and in some subjects specific abnormalities in lipid metabolism may accentuate the predisposition to arteriosclerosis. It is not unlikely that many people do have transitory periods of absolute or relative hypercholesterolemia which remain unrecognized and these may suffice to initiate aortic lesions which leave permanent scars. There is a distinct possibility that not cholesterol itself but some substance related to cholesterol is immediately responsible for the initiation of aortic lesions, a possibility now under investigation despite the difficulties arising from our very imperfect knowledge of the intermediary metabolism of cholesterol. In any event the evidence relating arteriosclerosis to a disordered cholesterol metabolism is too suggestive to be ignored.

The direct attack upon arteriosclerosis as it occurs in man is still in the exploratory stage. As there is no way to quantitate intimal atheromatosis and, therefore, to judge the effects of prophylactic and therapeutic agents, it has been necessary to resort to determination of the blood levels of cholesterol and other lipids, a very tangential approach. This has, however, already yielded some result. It would appear that the serum cholesterol levels in patients with overt coronary arteriosclerosis tend to be significantly higher than in apparently normal subjects of the same age group, and also that the levels fluctuate much more widely. It has been known for some time, of course, that the diseases associated with marked and sustained hypercholesterolemia are frequently complicated by the precocious development of extensive arteriosclerosis.

Studies in man of the effects of diets high in cholesterol and fat indicate that they have surprisingly little influence upon serum cholesterol levels. This is not due to failure to absorb cholesterol since estimation of the fecal sterol content in such experiments has revealed that man has an unexpectedly large capacity to absorb dietary cholesterol in the form of egg-yolk powder. How much of the absorbed cholesterol is then metabolized and how much deposited in the tissues, a crucial point, has not, however, been possible of determination. It is uncertain, therefore, just what role the level of preformed cholesterol consumption may play in the production of arteriosclerosis.

The effects of low cholesterol, low fat diets have not yet been adequately studied. There are indications that the serum cholesterol levels may decline somewhat, at least temporarily; the effects on intimal lipid deposits are not known. Since acetate precursor for synthesis is readily available in dietary fat, protein and carbohydrate, restriction of preformed cholesterol in the diet may well have a limited although perhaps limiting effect.

At the present time attempts to prevent or minimize the development of arteriosclerosis in man would seem to be largely dependent upon the progress of animal experiments. These have arrived at the stage where it is possible to standardize the conditions necessary to induce arteriosclerosis regularly so that possible prophylactic or therapeutic agents, for example lipotropic agents, can be tested under reasonably controlled conditions. Such systematic programs are now being organized.

Clinico-pathologic Conference

Hepatosplenomegaly, Jaundice, Anemia and Recurrent Fever*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, Jr., M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, J. H. Y., (B. H. No. 161904), a fifty-two year old white, married farmer, entered the Barnes Hospital on July 30, 1948, complaining of fever, weakness and weight loss. The patient was somewhat obtunded at the time of admission but fragmentary information was secured from him and from his daughter. The family history was apparently irrelevant. In regard to the past history it was stated that the patient had had typhoid fever many years before admission and that he occasionally had mild respiratory infections; otherwise, he apparently enjoyed excellent health and for many years had done hard physical labor while working his farm. He suffered a traumatic injury to his left eye many years ago.

Two years before admission to the Barnes Hospital the patient began having episodes of weakness. He consulted his physician several times and was told that he had "low blood pressure." One year before entry he noted numbness of both his lower extremities and his gait became unsteady; he complained that unless he could see them he was unaware of the position of his feet. Eight months before coming to the hospital he developed a febrile episode which lasted one week and which was diagnosed by his physician as "flu." Two months later chills and fever associated with nausea and vomiting appeared and persisted for two to three weeks. Diagnosis of malaria was made and quinine was prescribed; the patient continued taking the drug daily until his entry to the Barnes Hospital. Subsequently the patient enjoyed a period of ten to fourteen days during which he was practically symptom-free. Attacks of chills and fever returned, however, and recurred repeatedly, each one lasting two to three weeks with periods of remission lasting one to two weeks; jaundice was thought to have been associated with some of the bouts. During the course of his illness penicillin was given on several occasions and six weeks before his entry to the Barnes Hospital he was taken to an outside hospital where he was said to have had "paralysis of the left arm and absent pain sensations in both legs." Severe anemia was discovered but only one blood transfusion was given since there was apparently considerable difficulty in finding suitable donors. After he left the hospital the patient was somewhat improved but for two months before entry he noted that his stools were black. One month before admission he developed pain in the right upper quadrant which recurred on several occasions and two weeks prior to entry there was slight epistaxis. About a week before his admission to the Barnes Hospital the patient developed high fever associated with almost continuous vomiting. During the course of his illness he had lost approximately 50 pounds.

Physical examination at the time of entry revealed the patient's temperature to be

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

40.5°c., pulse 100, respirations 24 and blood pressure 90/60. The patient was a well developed but extremely emaciated male who appeared acutely ill. His skin was dry, pale, loose and hot, and signs of dehydration were pronounced. There was no significant lymphadenopathy. The conjunctivae were pale. The pupils reacted well to light and accommodation. There was an opacity of the lens of the left eye. Examination of the right optic fundus showed the vessels to be essentially normal, but one small, fresh hemorrhage was noted. The tongue was red and dry. The teeth were badly decayed. There was no distention of the neck veins and the trachea was in the midline. Examination of the lungs revealed them to be clear to percussion and auscultation. The heart was normal in size and contour and the rhythm was regular. The sounds were rather distant and there was a grade II systolic murmur. The liver edge was felt 8 cm. below the costal margin and was smooth and firm. The spleen extended 12 cm. below the left costal border and its edge likewise was firm. Rectal examination was negative. Neurologic examination revealed complete absence of all tendon reflexes but the sensory examination was unsatisfactory.

The laboratory data were as follows: Blood count: red cells, 1,900,000; hemoglobin, 4.5 Gm. per cent; white cells, 3,800; differential count: stab forms, 6 per cent; segmented forms, 54 per cent; lymphocytes, 36 per cent; monocytes, 4 per cent. Urinalysis: specific gravity, 1.010; albumin, 1+; sugar, negative; sediment, occasional red blood cell. Stool: guaiac negative. Blood Kahn test: negative. Blood chemistry: sugar, 106 mg. per cent; non-protein nitrogen, 50 mg. per cent; total protein, 6.8 Gm. per cent; albumin, 2.8 Gm. per cent; globulin, 4.0 Gm. per cent; chlorides, 90 mEq./L.; carbon dioxide combining power, 25 mEq./L.; cephalin-cholesterol flocculation test, 4+; icterus index, 10 units; thymol turbidity greater than 24 units. Electrocardiogram: low T waves in leads I and II.

Immediately upon admission to the hospital the patient was given parenteral fluids and penicillin therapy was instituted. He likewise received large doses of vitamin B complex and vitamin C parenterally. Hematologic consultation was requested and the red count, white count and differential were found to be essentially those recorded during the routine admission studies. The platelet count was 585,000, the reticulocytes, 1.8 per cent. The cell indices were as follows: mean corpuscular volume, 80 cu. micra; mean corpuscular hemoglobulin, 27 gamma gamma; mean corpuscular hemoglobin concentration, 34 per cent. Sternal marrow aspiration was performed and revealed a normal number of granulocytes with toxic granulation, marked decrease in the erythroid elements and a definite increase in the number of plasma cells and reticulum cells. There were many small, round cells, the identity of which was not clear.

Further laboratory studies performed at this time were as follows: Agglutinations against tularense, brucella and typhoid antigens were negative; the circulation time (decholin) and venous pressure were within normal limits. Examination of the urine revealed that it contained bile but no Bence-Jones protein. The blood calcium was 9.4 mg. per cent; the phosphorus 5.2 mg. per cent; alkaline phosphatase, 9 Bodansky units; acid phosphatase, 3.9 King-Armstrong units and the chlorides, 103 mEq./L.

On the third hospital day the patient was typed and found to belong to group A, Rh positive. He was given two whole blood transfusions without immediate reaction, but on the following day jaundice was noted and the icterus index rose to 52.5 units. At that time the van den Bergh test was as follows: sodium bilirubinate, 6.3 mg. per cent; bilirubinglobin, 3.5 mg. per cent. Skin tests were performed with first and second strengths of purified protein derivative and with histoplasmin and coccidioidin; all were negative. Because the patient's temperature continued to be very high despite adequate penicillin dosage, he was started on streptomycin therapy on the

fifth hospital day, receiving a total dose of 1.2 Gm. daily. Desoxycorticosterone acetate was given in an attempt to correct persistent hypotension.

In the first three to four days of his hospital stay the patient continued to be somewhat obtunded but subsequently his sensorium cleared. On the sixth day a lumbar puncture was performed; the dynamics were normal as were the cell count, protein, colloidal gold curve and Wassermann. The temperature continued to range around 39°c. although occasionally it fell temporarily to lower levels. On the day before death repeat blood studies revealed the red count to be 2,070,000, hemoglobin, 5 Gm. per cent and white count, 3,400; the non-protein nitrogen had fallen to 32 mg. per cent, the carbon dioxide combining power was 27 mEq./L. and the chlorides were 101 mEq./L. The icterus index was 25 units and the total bilirubin was 3.2 mg. per cent. Repeated blood cultures were negative. On the final hospital day, August 7, 1948, the patient complained of being chilly; that night his temperature was 39.1°c. but he had no unusual complaints. Late that evening he called for a bed pan and when the nurse saw him a few minutes later he was dead.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Before we undertake discussion of this case I shall ask Dr. Grunow to comment on the x-ray films.

DR. OTTO H. W. GRUNOW: The chest film was not remarkable. The trachea was in the midline, the great vessels showed normal width and contour and the heart was not enlarged. There was no hilar adenopathy and both lung fields were entirely clear. An open film of the abdomen showed a small area of density in the right upper quadrant which conceivably represented a gallstone. Although the liver edge was described as extending 8 cm. below the costal margin, it did not appear abnormally large in the film. The kidney shadows were not outlined too well but the left kidney appeared to be displaced downward. The splenic flexure of the colon was likewise depressed by a large mass in the left upper quadrant, presumably the spleen, but which conceivably might lie in the tail of the pancreas. Films of the lumbar spine were within normal limits.

DR. ALEXANDER: This case presents a difficult diagnostic problem, characterized by fever of unknown origin associated with anemia and hepatosplenomegaly in an acutely ill patient. This patient was also said to have had a systolic murmur and I should like to begin by asking Dr. Smith whether he thinks that a diagnosis of subacute bacterial endocarditis should be entertained.

DR. JOHN R. SMITH: Whenever a cardiac murmur is audible in a patient who has fever, splenomegaly and the other signs which were seen here, one must certainly consider that diagnosis. In this particular case, however, I do not believe that the diagnosis is very probable.

DR. ALEXANDER: The fact that this patient had a murmur, fever, a retinal hemorrhage and occasional red cells in the urine all suggest to me the diagnosis of bacterial endocarditis possibly due to one of the less common organisms. In the last few years at these conferences we have seen atypical cases of endocarditis due to fungi such as Histoplasma capsulatum or Actinomyces.

DR. THOMAS H. HUNTER: It would be most extraordinary for subacute bacterial endocarditis to continue for two years without any cardiac enlargement, pulmonary congestion or signs of cardiac failure.

DR. ALEXANDER: Dr. Massie, what is your view on this point?

DR. EDWARD MASSIE: I would agree with Dr. Hunter.

DR. W. BARRY WOOD, JR.: Is not leukopenia rather uncommon in subacute bacterial endocarditis?

DR. MASSIE: Yes, it certainly is but I have seen an occasional case in which leukopenia was present.

DR. ALEXANDER: Let us now consider the signs of liver disease. This man certainly had disturbed liver function. Dr. Duden,

would you comment on the possibility that the liver was primarily involved in the disease process?

DR. CHARLES W. DUDEN: Certainly hepatomegaly, splenomegaly, abnormal bleeding and signs of disturbed liver function lead one to consider diseases of the liver such as hepatitis or even cirrhosis, but I doubt that either of these represented the primary diagnosis.

DR. ALEXANDER: The patient had intermittent jaundice and the flat film of the abdomen showed a shadow which could have been a gallstone. Likewise, he had pain in the right upper quadrant. Dr. Scheff, could this man have had biliary obstruction with infection?

DR. HAROLD SCHEFF: I do not believe that the clinical picture observed here could possibly have been secondary to biliary obstruction. I should like to suggest Hodgkin's disease as a possibility.

DR. ALEXANDER: That is a very good suggestion but before we take it up I should like Dr. Moore to comment on the liver function tests and on the recurrent jaundice.

DR. CARL V. MOORE: Since there was an increase in both the sodium bilirubinate and sodium bilirubinglobin, I would be inclined to believe that this patient had intermittent biliary obstruction and hepatogenous jaundice.

DR. ALEXANDER: In addition to subacute bacterial endocarditis are there any other infectious diseases which should be considered?

DR. CARL G. HARFORD: Actually I do not believe this patient had an infectious disease but on the basis of the data at hand histoplasmosis should be considered.

DR. ALEXANDER: Your point is well taken in view of the clinical picture. If this patient indeed had had histoplasmosis, Dr. Moore, when the bone marrow studies were done, would it not have been likely that the organism would have been found?

DR. MOORE: With the exception of one case at the Children's Hospital, we have never found histoplasma by bone marrow aspiration. I have, however, seen cases in other clinics in which the diagnosis was substantiated by that procedure. I am confident that had this man had histoplasmosis the organism would have been recovered from his bone marrow in view of the marked involvement of that tissue. I think we can say that this man had a granulomatous disease but I am not able to define the specific one at this time.

DR. ALEXANDER: Why do you believe that a granulomatous process is a most probable diagnosis?

DR. MOORE: The presence of persistent high fever, leukopenia without shift to the left in the presence of abnormal cells in the bone marrow, hepatomegaly, splenomegaly and involvement of the gastrointestinal tract all point to such a disease.

DR. ALEXANDER: I think you make a strong case for one of the so-called granulomas. Let us consider a few other diagnoses if only to eliminate them. Is undulant fever a very likely possibility, Dr. Harford?

DR. HARFORD: This patient's course would have been quite unusual for undulant fever since it was severe and progressive. Almost all of the signs are much more severe than would usually be expected in brucellosis.

DR. ALEXANDER: Would one not have expected the blood cultures to have been positive had this patient had brucellosis?

DR. HARFORD: Yes, the likelihood of the organism having been recovered upon repeated blood cultures would have been good although, of course, negative blood cultures do not completely rule out the disease.

DR. ALEXANDER: What about the agglutination test?

DR. HARFORD: The negative agglutination test also constituted evidence against the diagnosis of brucellosis, particularly at this advanced stage.

DR. MOORE: I should like to ask Dr. Harford about the results of the skin tests for tuberculosis, histoplasmosis and coccidiodomycosis. Should doubt be cast on the negative skin tests in view of the extreme severity of this man's illness?

DR. HARFORD: It is probably true that skin tests are less reliable in a terminal illness; especially in tuberculosis a so-called anergic state is said to occur in the agonal stage of the disease.

DR. MARGARET G. SMITH: At the Children's Hospital recently a child who at autopsy was found to have histoplasmosis had repeatedly negative skin tests with histoplasmin.

DR. ALONZA L. FARR: There are recent reports in the literature of patients with proven histoplasmosis who had positive skin tests. In these patients, however, the skin tests were usually performed repeatedly and it is conceivable that the positivity was due to development of hypersensitivity not as a result of the disease *per se* but rather because of repeated exposure to the test antigen. There is also a report of nine patients with fatal histoplasmosis in five of whom histoplasmin skin tests were negative. Since a very large percentage of the population in this part of the country have positive histoplasmin skin tests, I do not see that too much stress can be placed on the results one way or the other.

DR. MASSIE: I should like to ask Dr. Moore to comment on the neurologic findings in regard to the anemia.

DR. MOORE: Nothing in the hematologic findings suggested the diagnosis of pernicious anemia. I believe that the neurologic findings were more likely due to multiple vitamin deficiency which the patient probably had for a long time and which may have been exaggerated by the persistent high fever. I am unable to explain the neurologic manifestations in terms of the blood findings.

DR. ALEXANDER: It was stated that when the patient was admitted to the outside hospital his arm was paralyzed. No evidence of such paresis was observed on his examination here.

DR. HARFORD: Is it conceivable that the fact that this patient took quinine for a long period of time may have given rise to a state of hypersensitivity which may have been responsible for the terminal illness?

DR. ALEXANDER: I have never seen hypersensitivity to quinine in my experience. Perhaps, Dr. Saunders would discuss this point.

DR. GEORGE M. SAUNDERS: We saw many natives in endemic malarial regions who had taken quinine for long periods of time without ever developing sensitivity.

DR. ALEXANDER: Let us now attempt to define further what granulomatous disease this patient may have had. Dr. Moore, you said that the bone marrow aspiration showed some unusual small cells. Are you now able to dilate further on their nature?

DR. MOORE: No, I cannot. They were either lymphocytes or so-called primitive cells. There is a great deal of discussion among hematologists in regard to the nature of the latter; they are frequently seen but I do not believe that they have specific diagnostic significance. The increase in reticulum cells and plasma cells was compatible with any granuloma.

DR. ALEXANDER: In view of the increase in plasma cells and the high serum globulin should multiple myeloma be considered?

DR. MOORE: I believe multiple myeloma is extremely unlikely.

DR. ALEXANDER: Dr. Scheff, you suggested Hodgkin's disease. On what features do you base your suggestion?

DR. SCHEFF: Anemia, hepatosplenomegaly and gastrointestinal symptoms may all be identified with Hodgkin's disease. Furthermore, the remittent fever brings to mind so-called Pel-Ebstein fever which is said to be particularly common in abdominal Hodgkin's disease.

DR. ALEXANDER: Is intermittent jaundice compatible with your interpretation?

DR. SCHEFF: It is not common but may occur if the liver is involved.

DR. ALFRED GOLDMAN: Is not jaundice in Hodgkin's disease more often due to so-called acute acquired hemolytic anemia?

DR. MOORE: Yes, that is correct. Hemolytic jaundice may occur in Hodgkin's disease. Occasionally, intermittent biliary obstruction is seen when enlarged lymph nodes impinge on the common bile duct.

It would be quite difficult to explain hepatogenous jaundice in Hodgkin's disease and I am not sure that I can suggest a suitable mechanism for it. It should also be remembered that this patient had an increase in jaundice after transfusion; that conceivably could have been due to homologous serum jaundice or perhaps the cells were hemolyzed following transfusion although they were compatible as far as cross matching was concerned.

DR. ALEXANDER: Is leukopenia of any aid in differential diagnosis?

DR. MOORE: No, it may occur in any granulomatous disease.

DR. WOOD: Dr. Moore mentioned granulomatous diseases and so far we have discussed histoplasmosis, brucellosis and Hodgkin's disease. What other granulomatous diseases was he considering?

DR. MOORE: The term may be used to include tularemia, paratyphoid fever or tuberculosis. I do not think that tuberculosis is a very good possibility.

DR. ALEXANDER: Dr. Fields, would you comment on the neurologic findings?

DR. WILLIAM S. FIELDS: If it had been possible to do a satisfactory sensory examination at the time that the patient was admitted to the hospital, we would perhaps be in a better position to discuss this point. His neurologic complaints began two years before admission, and at one time he was said to have had paralysis of one arm. The earlier findings suggest involvement of the dorsal lateral portion of the cord, but the improvement is hard to explain.

DR. DUDEN: Although there is much against a diagnosis of pancreatic malignancy, some of the findings would be in keeping with that possibility. Carcinoma of the body or tail of the pancreas is often identified with idiopathic venous thromboses, and it is conceivable that portal vein thrombosis could have given rise to the large liver and spleen and that venous thromboses in the cord might have explained the neurologic findings.

DR. ALEXANDER: I think that is a very interesting suggestion.

A STUDENT: Does the presence of toxic granulation rule out malignancy?

DR. MOORE: Since many forms of malignancy may give rise to persistent fever and since fever is often identified with toxic granulation of the polymorphonuclear leukocytes, I do not think that the finding is of any value in differential diagnosis.

DR. ALEXANDER: Dr. Goldman, Dr. Moore dismissed tuberculosis as an unlikely possibility. What is your belief on this point?

DR. GOLDMAN: In this particular case tuberculosis in the absence of any pulmonary involvement would be most unusual. We have seen it limited to the spleen and liver and when it does involve the liver abnormalities in the peripheral blood frequently occur. I think the negative purified protein derivative skin tests mitigate against the diagnosis of tuberculosis despite the fact that in terminal cases anergy occasionally does occur.

DR. SAMUEL B. GUZE: I have seen cases in which the Division of Hematology has made a diagnosis of reticulum cell sarcoma, presumably on the basis of bone marrow studies. In this case reticulum cells were described in the bone marrow smear. Would Dr. Moore comment on the factors involved in arriving at the diagnosis of reticulum cell sarcoma on the basis of bone marrow findings?

DR. MOORE: If we made a diagnosis of reticulum cell sarcoma on the basis of the bone marrow examination alone, we were probably over confident. The only time that such a diagnosis can be made on that basis is when the number of reticulum cells is very great and when there are easily demonstrable mitotic figures within the reticulum cells themselves.

DR. ALEXANDER: Dr. Moore, which of the so-called lymphoma group would you think was the most likely considering all of the evidence here?

DR. MOORE: I think the findings are more in keeping with Hodgkin's disease than they would be with any of the other forms of lymphomas such as reticulum cell sarcoma or lymphosarcoma.

DR. WOOD: On one occasion when this patient had a temperature of approximately 40°C. he was given 1.2 Gm. of aspirin and his temperature fell dramatically to within normal limits. Sometime ago we had another patient with Hodgkin's disease with a high temperature and following a similar dose of aspirin his temperature fell to 35°C. At the time we consulted the literature and found that patients with Hodgkin's disease who have fever may be very sensitive to the antipyretic action of salicylates. Perhaps our observation in this case adds further evidence in favor of the diagnosis of Hodgkin's disease.

DR. ALEXANDER: Do you favor Hodgkin's disease, Dr. Wood?

DR. WOOD: Yes, I believe this man had a granulomatous disease, probably one of the lymphomas and among the lymphomas I would rate Hodgkin's disease the most likely.

DR. ALEXANDER: In summary then, this acutely ill patient with fever, hepatomegaly, splenomegaly and severe anemia is thought probably to have had Hodgkin's disease, but other granulomatous diseases, such as histoplasmosis, tuberculosis and brucellosis, have been considered and malignancy of the tail and body of the pancreas has also been mentioned. We shall ask the pathologists to clarify the situation for us.

Clinical Diagnosis: Hodgkin's disease.

PATHOLOGIC DISCUSSION

DR. ELI M. NADEL: At autopsy the axillary, cervical and inguinal lymph nodes were not enlarged. There were 500 cc. of fluid in the right pleural cavity and 350 cc. in the left.

The lungs weighed 1,900 Gm. There were a few fibrous adhesions on the lateral surface of the upper lobe of the right lung. Grey, confluent, fibrinous areas were present in both lungs together with a moderate amount of emphysema, congestion and edema. The tracheobronchial lymph nodes were moderately enlarged. Acute tracheobronchitis was present.

The pericardial sac contained 30 cc. of clear fluid. The heart weighed 350 Gm.; the cut surface of the myocardium was pale and the entire organ was moderately flabby. A few small, fibrous adhesions of the pericardium were noted in the atrioventricular groove.

The peritoneal cavity contained 250 cc. of clear fluid. A few fibrous adhesions were present between the omentum, gallbladder, liver, duodenum and colon. There was a calcified omental tag adherent to the gallbladder. The liver was markedly enlarged, weighing 2,780 Gm. The surface was smooth and the cut edge was pale, showing uniform enlargement and prominence of the individual lobules. The spleen was markedly enlarged; it weighed 1,370 Gm. The capsule over its lateral surface had a puckered, calcified area of thickening 3 cm. in diameter. The cut surface of the spleen was soft and bulged and there were many fairly well defined grey areas having an average diameter of 3 to 4 cm. The splenic pulp was congested.

Both kidneys were enlarged; the left weighed 240 Gm. and the right 210 Gm. Both capsules were moderately adherent. There was congestion in the cortex and medulla but the corticomedullary junction was well defined. There was generalized mottling of the surface by confluent grey areas. Over the surface of the upper pole white areas were seen. The pelves and ureters were grossly normal.

The adrenals were small, weighing together only 11 Gm. The cortices were thin and poor in lipids.

There was moderate enlargement of all of the retroperitoneal and peripancreatic nodes. Nodes along both curvatures of the stomach and in the protahepatic regions were similarly enlarged but the mesenteric nodes were not remarkable in size. The enlarged nodes were discrete, movable, elastic and on cut surface showed a predominance of grey uniform tissue.

Congestion, ecchymoses and petechiae were noted in the mucosa of the urinary bladder and gastrointestinal tract.

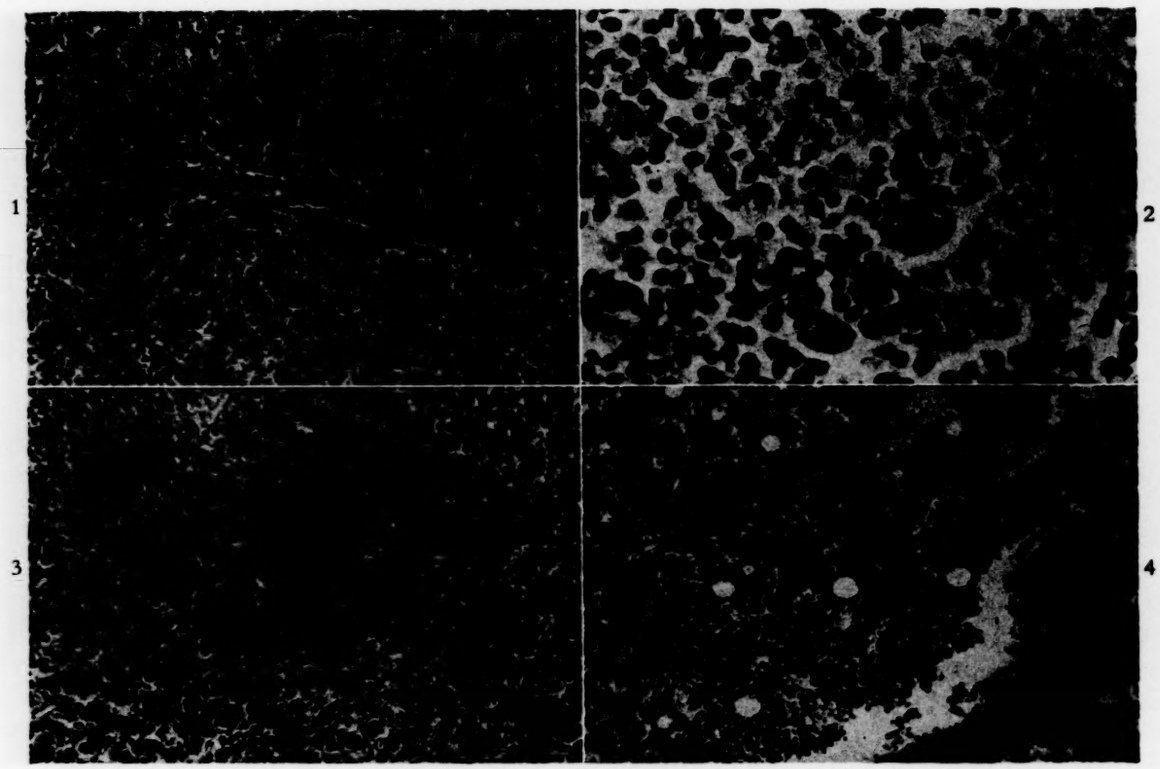


FIG. 1. Fibrosis and infiltration of Hodgkin's tissue with multinucleated giant cells in the spleen.
FIG. 2. Multinucleated giant cells, with prominent nucleoli and chromatin of the typical Reed-Sternberg type, and plasma cells in a section of spleen. Similar cells were present in lymph nodes, bone marrow, lungs, liver and kidneys.
FIG. 3. Focus of involvement of the bone marrow by Hodgkin's disease.
FIG. 4. Sections of hyperplastic bone marrow from portions not directly involved by Hodgkin's disease.

DR. MARGARET G. SMITH: On the basis of the gross findings we were not ready to make a definitive diagnosis. So large a spleen with such minimal involvement of the abdominal lymph nodes is certainly unusual in Hodgkin's disease. Figure 1 is a moderately low power photomicrograph of the spleen; it shows an increase of fibrous tissue around the small arterioles and loss of the normal architecture of the spleen. A considerable number of very large cells may be seen. In Figure 2 these large cells are shown under higher power; they are characterized by multiple nuclei, prominent nucleoli and definite nuclear membranes. Other similar cells having a single nucleus are also present as are a considerable number of plasma cells and lymphocytes; there is only an occasional eosinophilic leukocyte. The number of plasma cells in the spleen and other organs was somewhat greater than one usually finds in Hodgkin's disease but cases have been described in which plasma cell infiltration was conspicuous. We made a diagnosis of Hodgkin's disease on the basis of the microscopic appearance of these two sections.

The next section (Figure 3) is from the bone marrow and the findings again are quite consistent with the diagnosis of Hodgkin's disease. There is an increase in collagen and in the large cells with vesicular nuclei and prominent nucleoli; again a considerable number of lymphocytes and plasma cells which are not seen well in this photograph were identified. Areas such as this one were quite widespread through sections of vertebral marrow. The next section (Fig. 4) is of uninvolved marrow and shows hyperplasia of the erythroid and myeloid elements. Even in such areas as this in which there was relatively normal blood formation

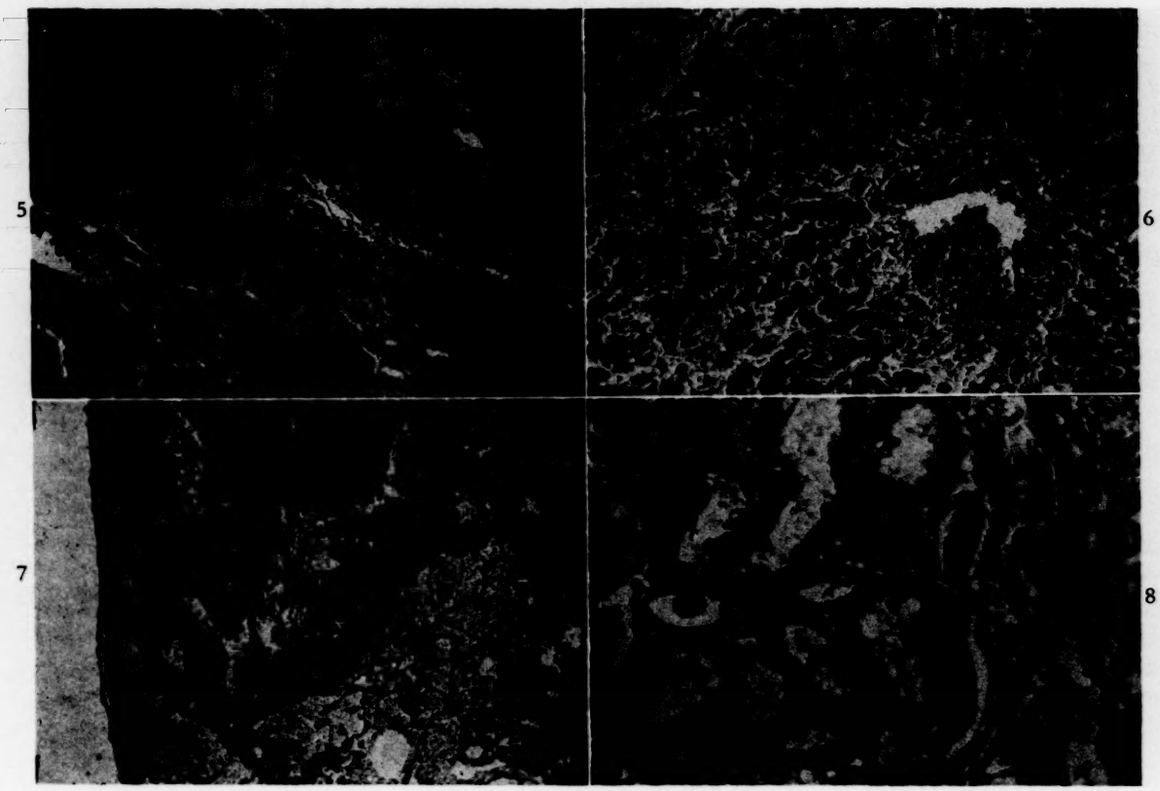


FIG. 5. Portal areas of the liver infiltrated by Hodgkin's disease and containing slight proliferation of small bile ducts.
FIG. 6. Infiltration and increased fibrous tissue in the portal spaces and central atrophy of the hepatic cords.
FIG. 7. Focus of involvement of the lung by Hodgkin's disease with congestion and edema of the uninvolved alveoli.
FIG. 8. Hemoglobin cast in one renal tubule and granules of iron in the epithelium of a tubule in the right upper corner.

plasma cells were present. Sections from some of the lymph nodes exhibited changes diagnostic of Hodgkin's disease but at least one node from the abdominal cavity showed practically no such change. In general there was minimal involvement of the lymph nodes but plasma cells were prominent.

In the periportal tissue throughout the liver there is infiltration of cells of types similar to those seen in other organs. (Fig. 5.) There is also marked atrophy of the hepatic cords in the central portions of the lobules, possibly associated with the severe anemia. Some fibrosis is present in the tissues about the portal zones and a little proliferation of the bile ducts in those areas is noted, again with the characteristic giant cells present. Figure 6 presents a higher power view of these findings.

In Figure 7 a small area of Hodgkin's tissue in the lung is shown. There is fibrosis in what appears to be a nodule of lymphoid tissue; plasma cells and the characteristic large cells of Hodgkin's disease are present. The marked edema in the alveoli represents a terminal phenomenon.

The kidneys were quite large and had a mottled appearance. Figure 8 shows a tubule deep in the cortex near the edge of the medulla. It contains a cast which had the brick red color characteristic of hemoglobin pigment. There is also destruction of the epithelium of this particular tubule. In the cells of an adjacent tubule very definite brown granules are present, probably iron. There is also swelling of the epithelium in the convuluted tubules and edema of the interstitial tissue. We thought that these findings were compatible with the changes of hemoglobinuric nephrosis

although of a very slight degree. A small nodule showing the characteristic changes of Hodgkin's disease was also present in the kidney.

This case had some unusual features. The microscopic observations were quite characteristic of Hodgkin's disease although the large number of plasma cells was somewhat unusual. Another uncommon feature was the limited and inconstant involvement of lymph nodes. There are several cases in the literature, however, in which only slight involvement of the lymph nodes was present. One such example was reported by Dr. Krumbhaar;[1] he cited a case in which although the spleen was very large there was no involvement of the lymph nodes. Another case was reviewed by Steiner in which there was involvement of the bones and liver with no involvement of the lymph nodes.[1]

Thus, despite the atypical gross aspects, the microscopic findings in this case were characteristic of Hodgkin's disease and a definitive diagnosis could be established.

Pathologic Diagnoses: Hodgkin's disease involving the spleen, bone marrow, liver, abdominal lymph nodes, lung and kidney; congestion and edema of the lungs; hydrothorax (right 300, left 350 cc.); hydroperitoneum (250 cc.); ecchymoses and petechiae in the gastrointestinal tract, urinary bladder and adventitia of the ascending aorta; hemoglobinuric nephrosis, slight.

Editor's Note: Reprints of these conferences are now available. Requests should be sent to Dr. Robert J. Glaser, Department of Medicine, Barnes Hospital, St. Louis 10, Mo.

[1] KRUMBHAAR, E. B. Hodgkin's disease of bone marrow and spleen without apparent involvement of lymph nodes. *Am. J. M. Sc.*, 182: 766, 1930.

[1] STEINER, P. E. Hodgkin's disease. *Arch. Path.*, 36: 627, 1943.

Case Report

Spontaneous Hemopneumothorax with Recovery*

VIRGIL J. DORSET, M.D. *and* LUTHER L. TERRY, M.D.
Baltimore, Maryland

ALTHOUGH spontaneous pneumothorax is a common condition, the sudden occurrence of blood and air in the pleural cavity of an apparently healthy individual is rare. In 1942 Hartzell[4] collected forty published cases with references and presented an excellent review of the literature on the subject. At the same time he reported four additional cases observed at the Cleveland City Hospital during a ten-year period. Further search of the literature prior to 1942 revealed four other cases not mentioned by Hartzell which were reported by Bouchut and Beaupere in 1924,[1] Doris in 1928,[2] Leggett, Myers and Levine in 1934[7] and Maxwell in 1938.[8] Since 1942, six additional cases have been reported by Tannenbaum,[11] Snively, Shuman and Snively,[10] Lea,[6] Payn and Lief,[9] Franklin[3] and Helwig and Schmidt.[5] The report of Helwig and Schmidt presented a review of the thirteen fatal cases upon which autopsy studies were available and added one case of their own.

Thus, medical literature contains reports of approximately fifty-four cases of spontaneous hemopneumothorax and autopsy findings on fourteen of those who died.

The following report is that of hemopneumothorax occurring in a healthy young individual who was carefully studied at the time and who has remained well for one year following the attack.

CASE REPORT

M. W. L., a twenty-seven year old white female employed as a surgical ward secretary in this hospital, was admitted August 4, 1946, complaining of pain in her left chest.

She stated that during the night of August 2, 1946, she noticed pain between her scapulae. The following day she had slight pain in her left chest, exaggerated at times by deep inspiration. A slight non-productive cough developed. When bending over, she noticed a "rolling sensation" in her left chest. On the evening of August 3rd she took a hot bath, felt better and went to a baseball game. Later that evening at home she experienced severe left chest pain which extended from the sternum to the vertebral column. The following day continued pain in the left chest and shoulder and a non-productive cough caused her to seek medical attention.

Past history revealed that the patient had had a similar attack of pain in her left chest in April, 1946 which lasted for eight hours. X-ray of the chest at that time showed no evidence of disease. She denied any past history suggestive of tuberculosis and denied any contact with tuberculous persons.

Physical examination disclosed a fairly well developed and well nourished white female twenty-seven years of age who was propped up in bed on pillows. Blood pressure was 134/94, temperature 37.2°C., pulse 120 and respirations 20. She appeared pale but not acutely ill and was not dyspneic at rest. Examination of the head and neck revealed no pertinent findings. Some lag of the left chest was noted on deep inspiration. There was dullness on percussion, absent vocal fremitus and distant to absent breath sounds over the lower left chest, especially posteriorly. No rales were heard. Heart size, sounds and rhythm were normal. The abdomen was soft and pliable. Some tenderness to pressure was noted at the left costovertebral angle. The liver and spleen were not palpable. The extremities were normal.

Laboratory data: Urinalysis was normal. Kline and Kahn serologic tests were negative. The platelet count was 340,000, bleeding time

* From the Medical Service of the U. S. Marine Hospital, U. S. Public Health Service, Baltimore, Md.

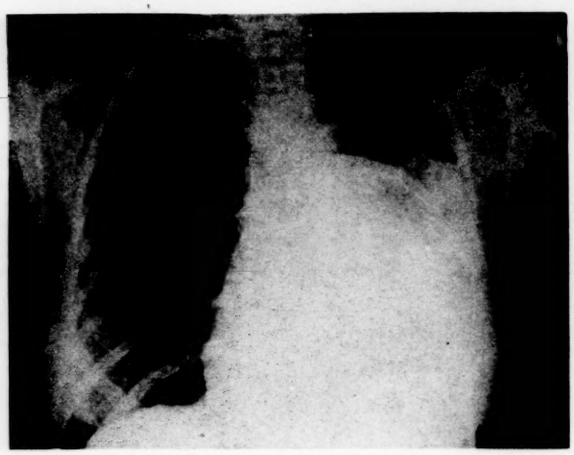


FIG. 1. X-ray of chest on admission showing hemopneumothorax on left.

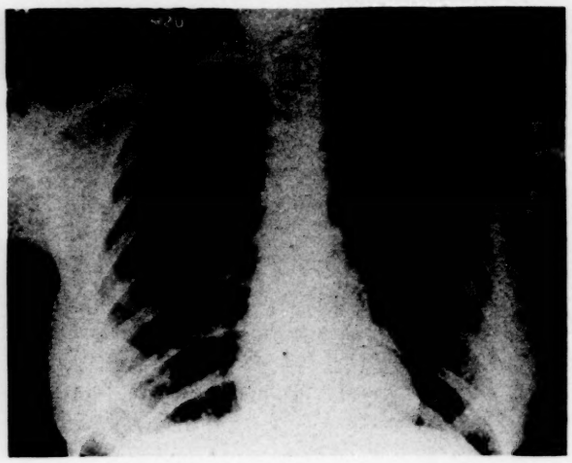


FIG. 2. X-ray of chest fourteen months after hemopneumothorax showing completely normal appearance throughout.

2 minutes, coagulation time by the tube method 9 minutes and prothrombin time 13 seconds, control 11 seconds.

X-ray of the chest on admission showed a left hydropneumothorax with the fluid level at the second interspace anteriorly. (Fig. 1.) The entire right lung was clear and the heart shadow was not significantly displaced. An electrocardiogram was within normal limits.

Shortly after admission a diagnostic thoracentesis was performed and revealed fluid which had the appearance of whole blood. Only 120 cc. was removed but the patient noted a considerable decrease in the left chest discomfort. Further aspirations were performed every few days and it was noted that the fluid gradually became less bloody. The date and quantities of fluid removed as compared with peripheral blood findings are shown in Table 1. There was no evidence of further bleeding after admission. Her temperature occasionally reached 37.6°C. (99.7°F.) during the first week of hospitalization but remained normal thereafter. Penicillin was given parenterally for the first nine days and 50,000 units were instilled in the chest at the time of each aspiration. Ferrous sulfate, multivitamins, ascorbic acid and vitamin K were given by mouth. There was a gradual rise in the hemoglobin and red cell count of the peripheral blood. The patient improved symptomatically as the amount of chest fluid decreased. She was discharged on the twenty-seventh hospital day, at which time x-ray revealed almost complete re-expansion of the lung with a small amount of fluid remaining in the left costophrenic sulcus.

On September 17, 1946, x-ray examination of the chest showed the lung fully expanded but a small amount of fluid still remained in the costophrenic sulcus. The patient was asymptomatic except for occasional mild discomfort in the left chest; the blood count was essentially normal. She was allowed to return to duty on October 7, 1946.

During the twelve months subsequent to the attack the patient was seen at frequent intervals and x-rays of the chest were obtained about every two months. A film on November 6, 1946, showed complete absorption of all fluid and x-rays showed both lungs to be completely clear on all occasions. An x-ray of the chest obtained on September 30, 1947, fourteen months after the initial attack, revealed normal lung fields. (Fig. 2.) Subsequent x-ray examinations, the last of which was taken on May 19, 1948, approximately twenty-one months after the onset, also were clinically negative. The patient has resumed her normal life and has remained well. She complained of occasional mild discomfort in the left chest but otherwise was completely asymptomatic.

Guinea pig inoculation with the chest fluid failed to show any evidence of tuberculosis. Skin test with the first test dose of purified protein derivative (0.00002 mg.) showed a positive reaction in forty-eight hours.

COMMENTS

Review of the literature on spontaneous hemopneumothorax reveals that all of the

previous cases but one have occurred in males. This is the second reported case in a female. The average age of all patients has been twenty-six years, with a range from seventeen to forty-four years of age.

The etiology of spontaneous hemopneumothorax is not clear but most authors believe that it is not different from spontaneous pneumothorax. They believe that the bleeding is simply a complication of the latter condition and that it is due to rupture of an emphysematous bleb or of a pleural adhesion. However, the majority of cases reported have not been associated with unusual physical or respiratory exertion. Other authors have attributed the condition to small unrecognized tuberculous lesions. Helwig and Schmidt,[5] in a recent review of the autopsy findings on fourteen cases, showed that the source of the bleeding was not demonstrated in half of the cases. However, the majority of the patients showed apical pleural scars and six had adhesions involving the lung. Emphysematous bullae were observed ten times, ruptured bullae four times and torn pleural adhesions five times. In many instances the origin of the pneumothorax was not determined and in three cases no lesions of the collapsed lung could be found.

The onset of symptoms in most reported cases was characterized by pain in the involved side of the chest followed in a few hours, or days in some instances, by weakness, dyspnea, pallor and faintness. The interval between the onset of pain and the signs of shock was apparently dependent upon the rate of blood loss. In some cases the presenting symptom was abdominal pain. Exploratory laparotomy was considered not infrequently and two patients were operated upon with negative findings resulting. Nausea, vomiting, diarrhea and pain in various parts of the abdomen were mentioned in several cases.

The physical findings were usually those of pneumothorax with fluid. Mediastinal shift was noted as a rule in cases of massive hemorrhage and was usually associated with a weak thready pulse, low blood pressure, sweating and dyspnea. Low grade fever and moderate to severe secondary anemia were found as a rule. The leukocyte counts varied from 6,000 to 20,000. Sputum examinations were invariably negative for acid-fast bacilli. Platelet counts,

TABLE 1

Date	Peripheral Blood				Aspirated Chest Fluid					
	Red Blood Cells	Hemoglobin	White Blood Cells	Sedimentation Rate (mm. hr.) (Wintrobe)	Red Blood Cells	Hemoglobin	White Blood Cells	Specific Gravity	Culture	Fluid Aspirated (cc.)
8–5–46	3,000,000	8.5	13,400	..	2,700,000	8	6,500	1.040	no growth	120
8-7-46	.....	....	.....	..	.....	..	....	.....	.....	250
8–12–46	3,000,000	10.0	11,600	..	.....	..	....	.....	.....	250
8-15-46	3,000,000	11.5	.....	..	.....	..	....	.....	.....	300
8-20-46	.....	....	.....	21	.....	..	....	.....	.....	400
8-23-46	.....	....	.....	..	.....	..	....	.....	.....	502
8-26-46	3,900,000	12.5	7,500	11	3,100	..	8,700	1.024	no growth	235
9-17-46	4,200,000	13			Total aspirated					2,057 cc.
11-6-46	.....	13	10,000	9						
8-4-47	4,640,000	12.5	12,500	14						

prothrombin, bleeding and coagulation times were normal when obtained.

The clinical course of most patients who survived the initial period of shock and who showed no signs of continued bleeding was that of gradual steady improvement and recovery without complications. However, fourteen of the fifty-four reported cases terminated fatally. No cases of recurrent spontaneous hemopneumothorax were found in the literature, in contrast to rather frequent instances of recurrent spontaneous pneumothorax.

The treatment of spontaneous hemopneumothorax was considered by most authors on this subject to depend upon the degree of hemorrhage and shock. It would appear that unless there is marked respiratory distress only a small amount of fluid should be removed initially for diagnostic purposes. In the event of continued bleeding transfusions of whole blood are indicated. Complete bed rest and sedation are important in the early stages. Signs of continued bleeding might possibly indicate the need for thoracoscopy and cauterization of the bleeding point. Once the first few critical days have passed aspiration of 200 to 500 cc. of blood should be done every few days, with partial replacement of the fluid by air. If the blood is not removed, calcification of the pleura and secondary cardiac complications may occur.

SUMMARY

1. A case of spontaneous hemopneumothorax in a twenty-seven year old woman who was apparently well prior to the attack is reported. Careful follow-up for fourteen months subsequently failed to reveal any evidence of pulmonary disease.

2. The literature on this relatively rare condition is discussed briefly, with relation to etiology, clinical course and treatment.

REFERENCES

1. Bouchut and Beaupere. Hemopneumothorax spontane chez un jeune sujet. *Lyon M.*, 138: 283–284, 1926.
2. Doria, R. Emopneumotorace spontaneo con versamento bloccato. *Riforma med.*, 44: 552–554, 1928.
3. Franklin, J. Spontaneous hemopneumothorax: report of a case occurring in a soldier. *Ann. Int. Med.*, 23: 437–441, 1945.
4. Hartzell, H. C. Spontaneous hemopneumothorax. *Ann. Int. Med.*, 17: 496–510, 1942.
5. Helwig, F. C. and Schmidt, E. C. H. Fatal spontaneous hemopneumothorax. *Ann. Int. Med.*, 26: 608–617, 1947.
6. Lea, R. G. Spontaneous hemopneumothorax, *Canad. M. A. J.*, 46: 371–373, 1942.
7. Leggett, E. A., Myers, J. A. and Levine, I. Spontaneous pneumothorax. *Am. Rev. Tuberc.*, 29: 348–361, 1934.
8. Maxwell, J. Spontaneous hemopneumothorax. *Brit. M. J.*, 1: 778, 1938.
9. Payn, S. B. and Lief, V. F. Spontaneous hemopneumothorax. *Bull. U. S. Army M. Dept.*, 3: 94–99, 1945.
10. Snively, D., Shuman, H. and Snively, W. D. Spontaneous hemopneumothorax. *Ann. Int. Med.*, 16: 349–356, 1942.
11. Tannenbaum, M. Spontaneous hemopneumothorax. *Dis. of Chest*, 8: 178–181, 1942.

CHOLINE (FLINT)

FOR A BETTER PROGNOSIS IN CHRONIC HEPATITIS

NUMBER 15 OF A SERIES

The production of bile and disturbances associated with abnormalities of bile physiology have long claimed the interest of the physician and investigator, but in recent years interest has extended beyond the secretory function of the liver.

Emphasis on maintenance of hepatic function now reflects the increased recognition of the relationship of the liver to the processes of excretion, the formation of blood, the clotting mechanism, the regulation of blood volume and body temperature, the storage of essential nutritive materials, the reticulo-endothelial defensive mechanism, the detoxication and conjugation of harmful waste products, and the metabolism of carbohydrates, proteins and the lipids. Attention toward restoration and maintenance of optimal hepatic activity has proved of practical value in therapy of many disorders involving disturbances of these non-secretory functions of the liver.

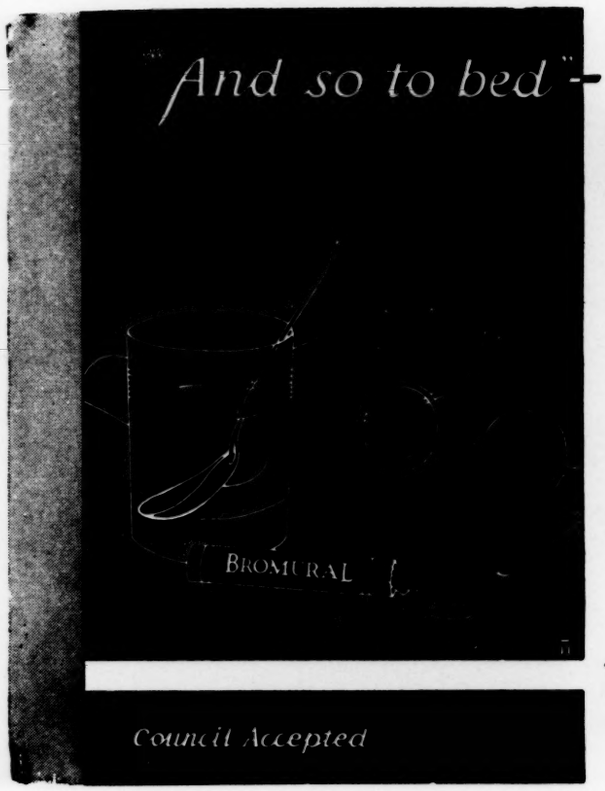
Syrup **Choline** Dihydrogen Citrate (Flint), a completely stable and palatable source of the lipotropic agent, **choline,** is indicated in conditions in which hepatic insufficiency may be associated with altered lipid metabolism.

Syrup **Choline** Dihydrogen Citrate (Flint)—25% W/V—containing one gram of **choline** dihydrogen citrate in each 4 cc., is supplied in pint and gallon bottles. The specification of Syrup **Choline** Dihydrogen Citrate (Flint) will insure the use of a **choline** product offering complete patient acceptance.

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

For your copy of The Present Status of **Choline** Therapy in Liver Dysfunction, write:

FLINT, EATON & COMPANY
DECATUR, ILLINOIS



BROMURAL

(alphabromisovalerylcarbamide)

A well tolerated hypnotic, inducing a restful sleep. Two tablets upon retiring or in wakefulness during the early morning hours. Contains no barbiturate.

5 grain Tablets and Powder.

BILHUBER-KNOLL CORP.
ORANGE, - - NEW JERSEY

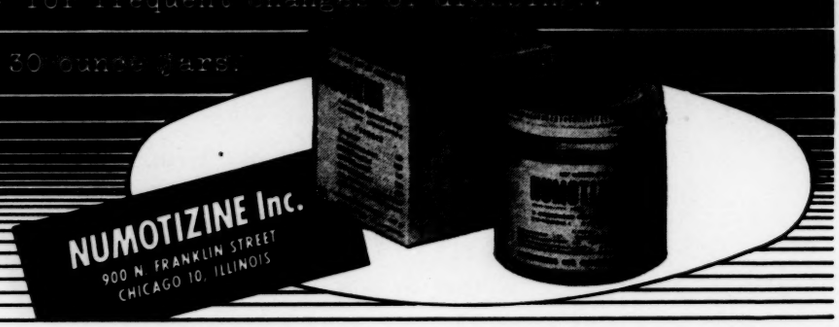
IN PHARYNGITIS TONSILLITIS COLDS

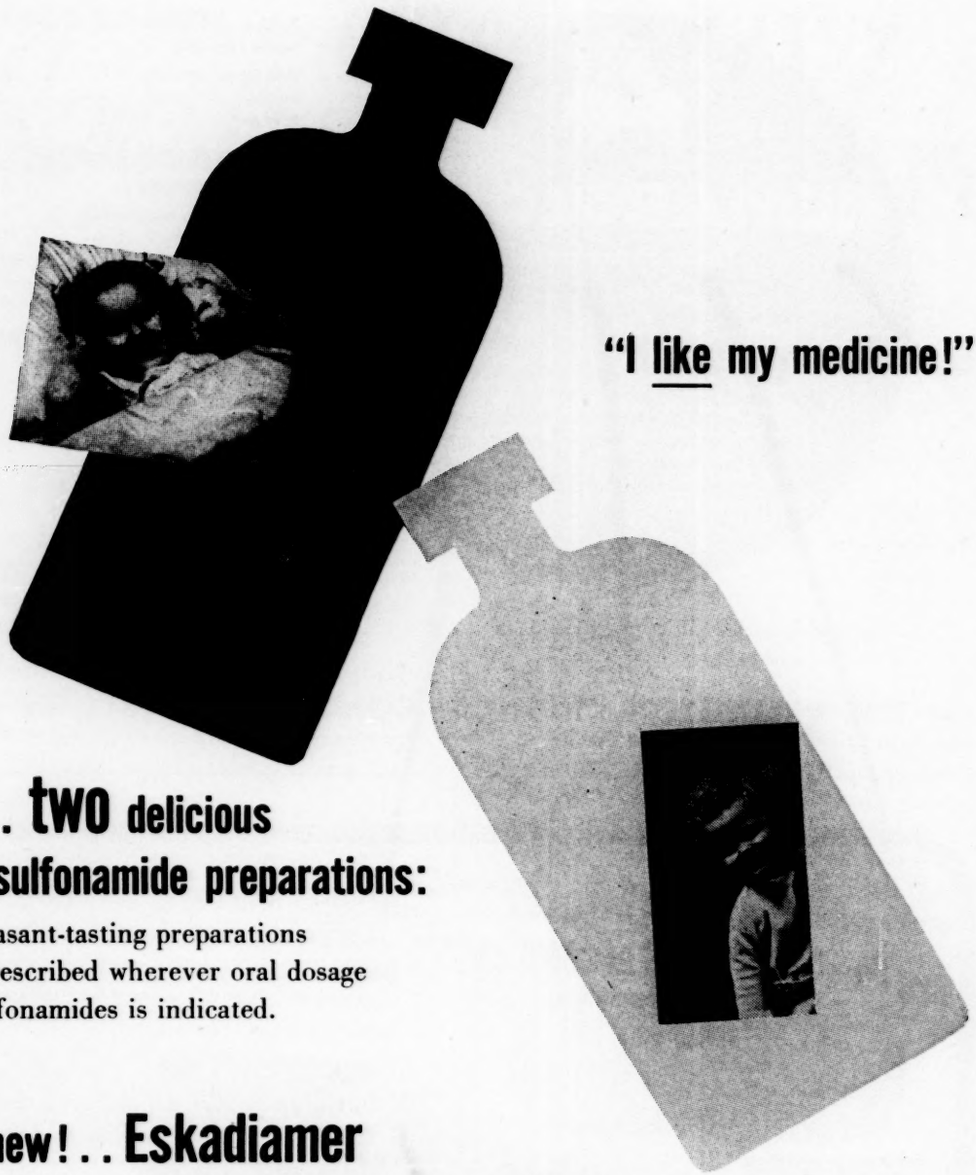
NUMOTIZINE

THE PRESCRIPTION CATAPLASM

... provides relief for eight hours or longer ... produces local anesthesia ... promotes increased circulation in the area, reducing congestion. With Numotizine there is no necessity for frequent changes of dressings.

4, 8, 15 and 30 ounce jars.





"I like my medicine!"

Now... two delicious S.K.F. sulfonamide preparations:

These pleasant-tasting preparations may be prescribed wherever oral dosage of the sulfonamides is indicated.

new!.. Eskadiamer

a *combination* fluid sulfonamide containing equal parts of sulfamerazine and sulfadiazine—the two safest sulfonamides in general use. Each 5 cc. (one teaspoonful) contains 0.25 Gm. (3.86 gr.) sulfamerazine and 0.25 Gm. (3.86 gr.) sulfadiazine.

Eskadiazine

the widely-prescribed fluid sulfadiazine which provides desired serum levels much more rapidly than sulfadiazine in tablet form. Each 5 cc. (one teaspoonful) contains 0.5 Gm. (7.7 gr.) sulfadiazine.

Smith, Kline & French Laboratories, Philadelphia

'Eskadiamer' & 'Eskadiazine' T.M. Reg. U.S. Pat. Off.

4 HEMABOLOIDS

(Iron Proteinate)

FORMULAS

Hematinic Therapy to Meet Individual Requirements

Presenting iron in readily assimilable protein combination. Cause no puckering, griping, gastric upsets, discoloration of teeth, or constipation.

Palatable • Well Tolerated

Tablets **HEMABOLOIDS** *with* Folic Acid

Each tablet represents:
Iron (as proteinate).....50 mg.
Folic Acid..... 5 mg.

HEMABOLOIDS *with* Liver Concentrate

Each fluid ounce represents:
Alcohol (by volume).....17%
Iron (as proteinate).....120 mg.
Liver Concentrate (20:1).....500 mg.
Cane sugar, glycerine, flavoring...ad...q.s.

Tablets **HEMABOLOIDS** *with* Liver Concentrate

Each tablet represents:
Iron (as proteinate)..... 35 mg.
Liver Concentrate (20:1).....100 mg.

HEMABOLOIDS ARSENIATED

Each fluid ounce represents:
Alcohol (by volume).....17%
Arsenous Acid.....1/20 gr.
Iron (as proteinate) .....120 mg.
Cane sugar, glycerine, flavoring...ad...q.s.

Arlington

THE ARLINGTON CHEMICAL COMPANY, YONKERS 1, NEW YORK

"...gel of granular discrete consistency."*

...not a mucilaginous mass

TO CORRECT CONSTIPATION WITHOUT IMPACTION

BASSORAN

STIMULATION WITHOUT IMPACTION—Swelling into a gel of granular, discrete consistency, rather than a uniform mucilage, Bassoran is less likely to impact and cause intestinal obstruction than other colloidal laxatives.*

BULK WITHOUT BLOAT— The bulking action of Bassoran occurs primarily in the intestine, thereby avoiding a sensation of "bloating" in the stomach.

ADSORPTIVE AND ANTACID ACTION—Bassoran also differs from other bulk producing agents by supplying magnesium trisilicate to neutralize excess acid and adsorb intestinal toxins.

BASSORAN Plain • BASSORAN with Cascara

Both forms at prescription and hospital pharmacies in 7-oz. and 25-oz. jars.

*Gray, H. and Tainter, M. L.: Colloid Laxatives Available for Clinical Use, Am. J. Dig. Dis. 8:130-139 (1941).

MERRELL

THE WM. S. MERRELL COMPANY • CINCINNATI, U. S. A.

Now! CHLOROPHYLL* AEROSOL THERAPY

the new advance in the Inhalation Treatment of Respiratory Tract Infections

CHLOROPHYLL AEROSOL THERAPY, as made possible by *Chloresium Aerosol Solution, enables the physician to provide the remarkable therapeutic effectiveness of chlorophyll in the inhalation treatment of both upper and lower respiratory tract infections. It is the result of intensive laboratory and clinical investigation to meet the long-felt need for an effective nontoxic, healing, decongestive, antibacterial and deodorizing agent for use in inhalation therapy.

For use with any standard nebulizing equipment

Chloresium Aerosol Solution is a specially processed preparation containing the purified therapeutically active *water-soluble* derivatives of chlorophyll "a" ($C_{55}H_{72}O_5N_4Mg$), designed for use with any standard nebulizing equipment. It is a natural, nontoxic, biotherapeutic agent and may be used either alone or, where indicated, as a solvent vehicle for penicillin or other antibiotic inhalation therapy.

A unique combination of advantages

Chloresium Aerosol Solution provides the following unique and fundamental advantages in inhalation therapy:

Absolutely nontoxic
Accelerates healing by stimulating normal cell metabolism
Decongests, promptly, without rebound phenomena
Exerts antibacterial effect, particularly on secondary saprophytic, proteolytic invaders
Does not interfere with ciliary activity; tends to restore normal motility if impaired
Can be used freely—especially valuable in the field of pediatrics
Deodorizes fetid, foul-smelling conditions
May be used as solvent vehicle for antibiotic inhalation therapy

Indicated for all respiratory tract infections

The value of Chloresium Aerosol Solution used alone or as vehicle for antibiotics has been demonstrated in the treatment of most infections of the respiratory tract including acute and chronic sinusitis, rhinitis, pharyngitis, ordinary coryza, ozena, acute and chronic laryngitis, bronchitis, bronchiectasis, lung abcesses and other deep-seated inflammatory conditions.

Chloresium
Aerosol Solution

ETHICALLY PROMOTED
Available at all leading drugstores

FREE—MAIL COUPON

RYSTAN CO., INC., Dept. JM-1
7 N. MacQuesten Parkway
Mt. Vernon, N. Y.

Please send me, without obligation, clinical samples of Chloresium Aerosol Solution and complete literature.

Dr._____

Address_____

City_____ Zone____ State_____